KETENE REACTIONS. I. THE ADDITION OF ACID CHLORIDES TO DIMETHYLKETENE. II. THE CYCLOADDITION OF KETENES TO CARBONYL COMPOUNDS

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Part I describes the addition of several acid chlorides to dimethylketene. The resulting 3-ketoacid chlorides were isolated and characterized. The reactivities of acid chlorides were found to parallel the parent acid pKa's. A reactivity order of ketenes toward acid chlorides was established. Dimethylketene is more reactive than ketene which is more reactive than diphenylketene. Attempts to effect the addition of an acid halide to a ketene produced by in situ dehydrohalogenation yielded α-halovinyl esters. The addition of acid chlorides to ketenes was concluded to be an ionic process dependent upon the nucleophilic character of the ketene α-carbon and the polarity of the carbon-chlorine bond in the acid chloride.

Part II describes the cycloaddition of several aldo-ketenes to chloral. The ketenes were generated in situ by dehydrohalogenation and dehalogenation of appropriately substituted acyl halides. Both cis- and trans-4-trichloromethyl-2-oxetanones are produced in the cycloadditions with the sterically hindered cis isomer predominating. Isomer
distributions were determined by vpc or nmr analysis of the reaction solutions. Production of the ketenes by dehalogenation resulted in enhanced reactivity of the carbonyl compounds. By dehalogenation dichloroketene-simple ketone adducts were obtained whereas these adducts cannot be made by in situ dehydrohalogenation. The isomer distributions and the fact that the distributions are insensitive to substituent effects, solvent effects, or method of in situ ketene preparation strongly suggests a near concerted process.
KETENE REACTIONS. I. THE ADDITION OF ACID CHLORIDES TO DIMETHYLKETENE. II. THE CYCLOADDITION OF KETENES TO CARBONYL COMPOUNDS

DISSERTATION

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By

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PART I

THE ADDITION OF ACID CHLORIDES

TO DIMETHYLKETENE
Chapter I

Introduction

The characteristic reactions of ketenes are addition reactions producing carboxylic acid derivatives, polymerization reactions, and addition reactions producing four membered rings (14).

The most well known of the ketene reactions are the additions of nucleophiles to produce carboxylic acid derivatives (14, pp. 1173-7).

\[ \text{R'R'C=C=O} + \text{HNu} \rightarrow \text{R'R'CHC-Nu} \]

Of the polymerization reactions of ketenes, the most common is dimerization. Aldoketenes, \( R_2 = \text{H} \), have been shown to give predominately the \( \beta \)-lactone dimer while the keto-ketenes normally produce cyclobutadione dimers (14, pp. 1182).

\[ 2 \text{R'R'C=C=O} \rightarrow \text{R'R'C=C=O or R'R'C=C=O} \]
Cycloaddition reactions of ketenes have been investigated extensively. Ketene-olefin cycloadditions have been shown to be concerted (2+2) additions and follow the conservation of orbital symmetry rules as stated by Woodward and Hoffmann (7, 4, 28). The cycloadditions of ketenes to imines (13, 16), enamines (10) and carbodiimides (2) have been shown to be stepwise additions with dipolar intermediates or combinations of concerted and stepwise additions.

Less is known about the addition of acid halides to ketenes than the above reactions. The addition occurs across the olefinic double bond, producing a 3-ketoacid halide (14, pp. 1178-80).

\[
\begin{align*}
R-C-X + (R)_2 C\equiv C=O & \rightarrow R-C-C(R)_2 C\equiv X
\end{align*}
\]

Staudinger and coworkers reported the reaction of diphenylketene with several acid halides in 1914 (25). Oxalyl chloride and bromide yielded diphenylmalonyl halides by addition to the ketene and decarbonylation.

\[
\begin{align*}
\phi_2 C\equiv C=O + X-C-C-X & \rightarrow [X-C-C-C(O)\phi_2 C\equiv X] \rightarrow (X-C\phi_2 C)\phi_2
\end{align*}
\]
Phosgene also produced diphenylmalonyl chloride under more severe conditions. Acetyl, benzoyl and succinyl chlorides yielded only diphenylketene polymers under similar conditions.

Sorm and coworkers found ketene to add acid halides activated by polar groups in the α-position (21). The 3-ketoacid chlorides were trapped as ethyl esters.

\[
\text{CH}_2\text{C}=\text{O} + R\text{-C-Cl} \xrightarrow{\text{C}_2\text{H}_5\text{OH}} R\text{-C-CH}_2\text{C}=\text{O}\cdot\text{C}_2\text{H}_5
\]

\[
R = \text{Cl-C-CH}_2, \text{CCl}_3, \text{Cl-C}, \text{C}_2\text{H}_5\text{-O-C}, \text{CHCl}_2, \text{CH}_3\text{C}^-. \]

The reactivity of the acid chlorides toward ketene, based on yields of the esters, decreased in the order shown. The reaction conditions, 0-60° in chloroform, were milder than those used by Staudinger with diphenylketene (25).

Sorm and coworkers found a correlation between parent acid pKa and reactivity of the acid chloride toward ketene (22). For example, the chloride of trichloroacetic acid, pKa 0.70, produced sixty-four per cent of the 3-ketoacid ester with ketene; the chloride of dichloroacetic acid, pKa 1.48, twenty-six per cent; and the chloride of chloroacetic acid, pKa 2.85, did not react.
Yields of the 3-ketoacid esters could be doubled if the reaction solvent was liquid sulfur dioxide (22).

More recently Stachel has reported the reaction of two moles of diethylketene with one mole of oxalyl chloride under mild conditions to produce derivatives of tetraethyl-3, 4-diketoadipic acid (23).

\[
2 \text{R}_2\text{C} = \text{C}=\text{O} + \text{Cl}-\text{C}-\text{C}-\text{Cl} \rightarrow \text{Cl}-\text{C}-\text{CR}_2\text{C}-\text{C}-\text{CR}_2\text{C}-\text{Cl}
\]

\[
\begin{array}{c}
\text{Cl} - \text{C} - \text{CR}_2 \\
\text{O} \\
\text{Cl}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{R}_2\text{Cl} \\
\text{O} \\
\text{Cl}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{R}_2\text{Cl} \\
\text{O} \\
\text{Cl}
\end{array}
\]

The tetraethyl-3,4-diketoadipoyl chloride initially produced slowly rearranged to the mono- and eventually to the bis-pseudoacid chlorides.

In the three cases cited above, the acid halides were reacted with ketenes which were isolated: diphenylketene was prepared by the dehydrochlorination of diphenylacetyl chloride and isolated (25); ketene was prepared by the pyrolysis of acetic anhydride and passed into the reaction mixture (21); and diethylketene was prepared by the pyrolysis of tetraethyl-1,3-cyclobutadione and isolated (23). Since the majority of the ketenes reported in the literature cannot
be isolated because of their extreme reactivity, they are prepared in situ with the substrate.

Runge and Koch have reported phenylacetyl chloride and oxalyl chloride when treated with triethylamine produce the lactone of pulvinic acid (20).

Although the authors make no mention of phenylketene as an intermediate in the reaction, the conditions are among those used to produce ketenes in situ, i.e., an acid halide with an α-hydrogen is treated with a tertiary base. From Stachel's work (23) it can be seen that the pulvinic acid lactone was the result of phenylketene reacting with oxalyl chloride to form diphenyl-3,4-diketoacidipoyl chloride, tautomerization of the chloride to the bispseudoacid chloride and loss of hydrogen chloride.
In view of the limited number and nature of these reports of the addition of acid halides to ketenes, a further investigation was warranted. While acid halide reactivity toward ketene had been related to parent acid pKa, no correlation had been made for any other ketene, nor had the reactivities of various ketenes toward the same acid halides been compared. Also, the extension of Runge and Koch's work (20) to halogenated ketenes was of interest.

Further investigation of the reaction was also prompted by its possible application as a general synthesis for 3-keto-acid halides. Relatively few of these compounds have been reported and a general synthesis is not known. Acetoacetyl chloride (12), chloroacetoacetyl chloride (11), and acetoacetyl fluoride (18) have been prepared by reacting diketene with hydrogen chloride, chlorine, and hydrogen fluoride. Others have been prepared by miscellaneous methods.

In order to add to the knowledge of this reaction, the following were proposed: (a) study of the reaction of a series of acid halides with demethylketene to correlate acid pKa with acid halide reactivity and compare the reactivity of dimethylketene with that of ketene, (b) react diphenylketene with other acid halides to add to the comparison of ketene reactivities and (c) investigate the addition of acid halides to haloketenes produced in situ.
Chapter II

Experimental

Infrared, (ir), spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer. Spectra were obtained using neat samples between sodium chloride discs or as approximately five per cent solutions in chloroform or carbon tetrachloride in 0.1 mm fixed thickness potassium bromide cells.

Nuclear magnetic resonance, (nmr), spectra were recorded on a Varian A-60 spectrometer. Spectra were obtained from carbon tetrachloride solutions with approximately one per cent tetramethylsilane as an internal standard, (δ = 0.00 ppm).

Mass spectra were obtained with a Hitachi RMU-6E mass spectrometer.

Melting points were obtained using a Thomas-Hoover capillary melting point apparatus. Melting points and boiling points are uncorrected.

Preparation of solvents and reagents. All solvents were dried by distillation from a drying agent such as calcium hydride and were stored over Molecular Sieves (4-A) under nitrogen.

The following reagents were purchased commercially: isobutyryl chloride, trichlorocacetyl chloride, acetyl chloride,
benzoyl chloride, triethylamine, tetramethyl-1,3-cyclobutadione and the carboxylic acids used in the preparation of the acid halides described below.

Acid halides were prepared by heating the acids with an appropriate halogenating agent. The acid halides were isolated and characterized by comparison of their boiling or melting points with those in the literature and by examination of their ir and nmr spectra. Diphenylacetyl, crotonyl, and α-chloropropionyl chlorides were prepared in good yields with thionyl chloride. Bromo- and chloroacetyl chlorides were prepared with phosphorous trichloride, and dichloroacetyl bromide was prepared with phosphorous tribromide. Dichloroacetyl chloride was prepared with chlorosulfonic acid (1).

Dimethylketene was prepared by the pyrolysis of tetramethyl-1,3-cyclobutadione (9). The dimethylketene thus obtained was free from the dimer and was used without further purification. Since dimethylketene forms dangerously explosive peroxides, it was prepared immediately before use (14, p. 1219).

The additions of acid halides to dimethylketene. The general procedure involved the addition of a 2M dimethylketene solution in hexane to an excess of the acid halide in hexane at room temperature. The reaction solutions were allowed to stand under a nitrogen atmosphere for several
hours. The hexane was removed at reduced pressure, and the residues distilled to yield the 3-ketoacid halides. The 3-ketoacid halides had very similar ir spectra with the acid halide carbonyl at 1790 cm⁻¹ and the ketene carbonyl at 1740 cm⁻¹. The boiling points, yields, and nmr data are listed in Table I. Isobutyryl and benzoyl chlorides gave no product even when heated for long periods with dimethylketene. The acid chlorides were recovered and dimethylketene dimer isolated.

Table I

Properties of the 3-Ketoacid Halides a

<table>
<thead>
<tr>
<th>R</th>
<th>Yield, %</th>
<th>Bp, °C (mm Hg)</th>
<th>nmr, δ</th>
</tr>
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<tbody>
<tr>
<td>I CCl₃-</td>
<td>61</td>
<td>68-9 (0.7)</td>
<td>1.77</td>
</tr>
<tr>
<td>II CHCl₂-</td>
<td>53</td>
<td>65-6 (1.0)</td>
<td>1.69, 6.30; 6:1</td>
</tr>
<tr>
<td>III CH₂Cl-</td>
<td>52</td>
<td>54-5 (0.65)</td>
<td>1.58, 4.32; 6:2</td>
</tr>
<tr>
<td>IV CH₂Br-</td>
<td>48</td>
<td>64 (0.35)</td>
<td>1.62, 4.24; 6:2</td>
</tr>
<tr>
<td>V CH₃CHCl₂-</td>
<td>35</td>
<td>53 (0.7)</td>
<td>1.55-1.65, 9:1 4.65</td>
</tr>
<tr>
<td>VI CH₃-</td>
<td>14</td>
<td>50 (5.0)</td>
<td>1.48, 2.25; 6:3</td>
</tr>
<tr>
<td>VII CH₃CH=CH-</td>
<td>12</td>
<td>63 (1.0)</td>
<td>1.46, 1.95, 6.25, 7.08; 6:3:1:1</td>
</tr>
<tr>
<td>VIII CHCl₂-</td>
<td>38</td>
<td>84 (0.3)</td>
<td>1.68, 6.30; 6:1</td>
</tr>
</tbody>
</table>

The 3-ketoacid chlorides were generally unstable at room temperature and were distilled only with some decomposition. Therefore, in most cases elemental analyses were not possible and derivatives were used for characterization.

**Methyl 4,4,4-trichloro-2,2-dimethyl-3-ketobutyrate, Ia.**
A 2 g (7.9 mmol) portion of I, was added dropwise with stirring to an excess of dry methanol at room temperature. Evaporation of the excess methanol and recrystallization of the solid residue from ligroine yielded 1.7 g, 91%, Ia: mp 42-3°; ir 1755 and 1740 cm⁻¹; nmr 3.75 $\delta$ (s) and 1.60 $\delta$ (s) in a ratio of 1:2.

**Anal. Calcd. for C₇H₉Cl₃O₃: C, 33.90; H, 3.63. Found: C, 33.75; H, 3.72.**

**4,4,4-Trichloro-2,2-dimethyl-3-ketobutyric acid, Ib.**
The dropwise addition of I to an excess of water resulted in a quantitative yield of Ib which was recrystallized from ligroine: mp 115-60°; ir 1170 cm⁻¹.

**Anal. Calcd. for C₆H₇Cl₃O₃: C, 30.86; H, 3.02. Found: C, 30.95; H, 2.72.**

**N-Benzyl-4,4,4-trichloro-2,2-dimethyl-3-ketobutyramide, Ic.**
To a solution of 3 mmol of I in 25 ml hexane was added dropwise a solution of 3 mmol benzylamine in 10 ml hexane. A white precipitate formed upon addition. The reaction mixture was washed with dilute hydrochloric acid solution followed by two water washes. Drying and evaporation of the solvent and
recrystallization of the residue gave 80% Ic: mp 101-2°; ir 1745 and 1635 cm⁻¹.

Anal. Calcd. for C₁₃H₁₄Cl₂NO₂: C, 48.40; H, 4.34.
Found: C, 48.45; H, 4.51.

N,N'-Dibenzyldimethylmalonamide, Id. Dropwise addition of 13.9 mmol of I with stirring to a solution of 46.7 mmol of benzylamine in 250 ml benzene gave a white precipitate. The reaction mixture was washed with dilute hydrochloric acid solution followed by several water washes. The benzene solution was dried over anhydrous magnesium sulfate, filtered and cooled to yield 81% of Id. Recrystallization from 70% ethanol yielded small white needles, mp 166-7°. A mixed melting point with an authentic sample of Id prepared from dimethylmalonyl chloride and benzylamine showed no depression.

Anal. Calcd. for C₁₉H₂₂N₂O₂: C, 73.50; H, 7.10; mol. wt. 310. Found: C, 73.50; H, 7.18; mol. wt. 310 by mass spectrum.

Id was also prepared by treating Ic with excess benzylamine.

N-Phenyl-4,4-dichloro-2,2-dimethyl-3-ketobutanamide, IIIa.
To a solution of 12.6 mmol of II in 50 ml of ether at 0-5° was added dropwise a cold solution of 25.2 mmol of aniline in 25 ml ether. The amine salt was filtered, and the solvent evaporated. The residue was recrystallized from 50% ethanol to yield 85% IIIa: mp 89-90°; ir 1740 and 1640 cm⁻¹.

Anal. Calcd. for C₁₂H₁₃Cl₂NO₂: C, 52.57; H, 4.81.
Found: C, 52.4; H, 4.70.
Using VIII, the same procedure gave IIa an 80% yield. A mixed melting point showed no depression.

N-Phenyl-4-chloro-2,2-dimethyl-3-ketobutyramide, IIIa. Using III and aniline, the procedure described for IIa gave 99% IIIa: mp 144-5°; ir 1740 and 1650 cm⁻¹.

Anal. Calcd. for C₁₂H₁₄ClNO₂: C, 60.13; H, 5.89. Found: C, 60.13; H, 5.94.

Methyl 4-bromo-2,2-dimethyl-3-ketobutyramide, IVa. Treatment of IV with excess methanol produced IVa in 80% yield: bp 64°(0.15 mm Hg), lit. bp 225-230° (5); ir 1740 and 1725 cm⁻¹.

Ethyl 2,2-dimethyl-3-ketobutyrate, VIa. The addition of VI to an excess of dry ethanol yielded 60% VIa: bp 50°(5mm Hg), lit. bp 185° (19); ir 1770 and 1730 cm⁻¹.

Comparison of the reactivities of dimethyl-, diphenyl- and phenylethylketenes. Diphenylketene was obtained by the dehydrochlorination of diphenylacetyl chloride with triethylamine (25). Phenylethylketene was prepared analogously using 2-phenylbutyryl chloride (6). Diphenylketene was combined with large excesses of trichloroacetyl chloride, dichloroacetyl chloride and dichloroacetyl bromide in separate benzene solutions. A control with the same concentration of diphenylketene as each of the samples was prepared. The concentration of diphenylketene in each sample was monitored by observing the ketene carbonyl peak in the ir spectrum, 2150 cm⁻¹. The samples and
control were heated at 60° for twenty-four hours after which there was no difference in the ketene concentrations in the control and samples. When combined with the same acid halides, dimethylketene reacted exothermically at room temperature in a matter of minutes. Phenylethylketene when heated with trichloro- and dichloroacetyl chlorides gave 2-phenylbutyryl chloride as the only isolable product.

**Attempted addition of an acid halide to dichloroketene.**

To a stirred solution of 320 mmol of dichloroacetyl bromide in 300 ml hexane at -78° were added 160 mmol triethylamine. After the dropwise addition was completed, the reaction mixture was allowed to warm to room temperature and remain overnight. Filtration of the reaction mixture under a nitrogen atmosphere yielded a theoretical amount of triethylammonium bromide. Removal of the hexane at reduced pressure and distillation of the residue gave 65% IX: bp 85°(1.5 mm Hg); ir 1790 and 1600 cm⁻¹; nmr 6.158, (s).

Anal. Calcd. for C₄H BrCl₂O₂: C, 15.9; H, 0.333.

Found: C, 15.6; H, 0.404.

**Reaction of IX with aniline.** Addition of less than a stoichiometric amount of aniline to a cold ethereal solution of IX followed by several water washes and evaporation of the ether yielded a solid. Recrystallization from 50% ethanol produced a good yield of 2,2-dichloroacetanilide, mp 119-120°; literature mp 117-118° (27).
Results and Discussion

The addition of acid chlorides to dimethylketene occurs smoothly. The resulting 3-ketoacid chlorides were isolated and characterized through physical and spectral data listed in Table I and derivatives.

\[
\begin{align*}
R-C-CI + (CH_3)_2C=CO & \rightarrow R-C-C(CH_3)_2C-Cl \\
R-C-C(CH_3)_2C-Cl + HNu & \rightarrow R-C-C(CH_3)_2C-Nu + HCl
\end{align*}
\]

Although they were unstable at room temperature, most of the 3-ketoacid chlorides could be kept for long periods at 0°C. The only 3-ketoacid bromide prepared, 4,4-dichloro-2,2-dimethyl-3-ketobutyryl bromide, VIII, was much less stable than the corresponding chloride, and the reaction of dimethylketene with dichloroacetyl bromide was much more vigorous than with dichloroacetyl chloride under the same conditions.

In preparing the N-benzylamide, Ic, of 4,4,4-trichloro-2,2-dimethyl-3-ketobutyryl chloride, I, an unexpected reaction occurred. When I was added to an excess of benzylamine, the
normal procedure for amide preparation, the product isolated was N,N'-dibenzylidimethylmalonamide, \( \text{Id} \), instead of the expected 3-ketoacidamide. The desired derivative, \( \text{Ic} \), could be made, however, by addition of less than a stoichiometric amount of benzylamine to \( \text{I} \). The conversion of \( \text{Ic} \) to \( \text{Id} \) could be accomplished by the treatment of \( \text{Ic} \) with excess benzylamine.

\[
\begin{align*}
\text{CCl}_3\text{C}-\text{C(CH}_3\text{)}_2\text{C}-\text{Cl} & \quad \overset{\text{excess}}{\text{CH}_2\text{NH}_2} \quad \overset{\phi}{\text{C}}\text{-NH}\text{-CH}_2\phi \\
\text{I} & \quad \text{Id}
\end{align*}
\]

This is an example of the haloform reaction in which the attacking base is benzylamine and the leaving group is the trichloromethyl anion.

Another unanticipated reaction occurred in the attempt to prepare and react dichloroketene in situ with dichloroacetyl bromide. Because of their great reactivity, the halo-ketenes have not been isolated. Rather these compounds have been prepared in situ and trapped as adducts of various keteneophiles. In an effort to react dichloroketene with dichloroacetyl bromide, one mole of triethylamine was added.
to two moles of dichloroacetyl bromide. The resulting product, IX, was 1-bromo-2,2-dichlorovinyl dichloroacetate, a member of a new class of compounds, \( \alpha \)-halovinyl esters. \( \alpha \)-Halovinyl esters, or acid halide enol esters, produce carboxylic acid derivatives very readily when reacted with nucleophiles under mild conditions. Thus, IX yielded dichloroacetonilide when reacted with aniline.

The \( \alpha \)-halovinyl esters occur as a result of acylation of the dehydrohalogenation intermediate. Base abstraction of a proton from the acid halide produces an enolate ion which is easily acylated by the excess acid halide.

\[
\begin{align*}
\text{CHCl}_2\text{CBr} & \xrightarrow{(\text{C}_2\text{H}_5)_3\text{N}} \begin{bmatrix}
\text{Cl} & \text{C} & \text{H}
\end{bmatrix}^+ \xrightarrow{\text{HN(C}_2\text{H}_5)_3} \text{CHCl}_2\text{CO-CBr} \quad \text{CHCl}_2\text{CBr}^+ \\
\text{CHCl}_2\text{CO-CBr} & = \text{CHCl}_2 \quad + \quad (\text{C}_2\text{H}_5)_3\text{NHBr}
\end{align*}
\]

The scope and mechanism of this reaction has recently been reported (3, 8, 15).

A correlation of parent acid pKa and acid chloride reactivity toward dimethylketene based on yields can be seen in Table II.
Table II

Parent Acid pKa and Acid Chloride Reactivity

<table>
<thead>
<tr>
<th>Parent Acid</th>
<th>pKa</th>
<th>Yield of 3-Ketoacid Chloride, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichloroacetic</td>
<td>0.70</td>
<td>61</td>
</tr>
<tr>
<td>Dichloroacetic</td>
<td>1.48</td>
<td>53</td>
</tr>
<tr>
<td>Chloroacetic</td>
<td>2.85</td>
<td>52</td>
</tr>
<tr>
<td>Bromoacetic</td>
<td>2.69</td>
<td>48</td>
</tr>
<tr>
<td>2-Chloropropionic</td>
<td>2.83</td>
<td>35</td>
</tr>
<tr>
<td>Acetic</td>
<td>4.75</td>
<td>14</td>
</tr>
<tr>
<td>Crotonic</td>
<td>4.69</td>
<td>12</td>
</tr>
<tr>
<td>Butyric</td>
<td>4.81</td>
<td>0</td>
</tr>
</tbody>
</table>

This corresponds to the relation found by Sorm and coworkers (22); however, dimethylketene is more reactive toward the same acid chlorides than ketene. Ketene did not react with chloroacetylc acid whereas dimethylketene produced a good yield of the 3-ketoacid chloride, III. Moreover, dimethylketene even reacts with acetyl chloride.

In comparing Sorm's work with ketene (21, 22) to that of Staudinger's with diphenylketene (25), it can be seen that ketene is more reactive toward acid chlorides than diphenylketene. The comparative reactions of diphenyl- and dimethylketenes with trichloro- and dichloroacetyl chlorides show diphenylketene to be much less reactive than dimethylketene. Thus the reactivity order toward acid chlorides, dimethylketene > ketene > diphenylketene, is established.
The addition of an acyl halide to a ketene might be considered a special case of the acylation of an olefin by an acyl halide. In such acylations the attacking species is considered to be the acyl cation, either as an ion pair or a strongly polarized complex (17). The site of attack on the olefin, the nucleophilic partner, is determined by inductive effects (Markownikov rule).

\[
\begin{align*}
\text{RC}=\text{O}^+ + \text{RCH}_2\text{CR}=\text{CHR}^- & \rightarrow \text{RCH}_2\text{CR}^+\text{CHR}^-\text{CR}^0 \\
\end{align*}
\]

The carbonium ion formed may lose a hydrogen ion to yield an \(\alpha,\beta\) - or a \(\beta,\gamma\) -unsaturated ketone or react with the halide ion to form a \(\beta\)-haloketone.

\[
\begin{align*}
\text{RC}=\text{O}^+ + \text{RCCR}=\text{CHR}^- & \rightarrow \text{RCCR}=\text{CHR}^- \\
\text{RCCHRCR}=\text{CHR}^- & \rightarrow \text{RCCR}^+\text{CHR}^- \\
\text{RCCHRCRXCH}_2\text{R}^- & \rightarrow \text{RCCHRCR}=\text{CHR}^- \\
\end{align*}
\]

The reaction is dependent upon the high electron density of the nucleophilic reagent and on the ease of formation and stability of the acyl cation.
In the case of the olefinic double bond in a ketene, the most nucleophilic carbon is the α-carbon. Analogous to the above mechanism, an attack by an acyl cation would give rise to another acyl cation. Reaction with a halide ion would produce a 3-ketoacid halide.

The available data do not exclusively indicate the acylation occurs through an acyl cation, and, in fact other mechanisms such as association of the ketene and acid halide in the transition state depicted below, cannot be eliminated.

\[
\begin{align*}
R'\text{C}^\alpha X + (R'_2)\text{C}=\text{C}=O & \rightarrow \text{R-C}^\delta - \text{X}^\delta \\
& \text{(R')}_2\text{C}^\gamma = \text{C}=\text{O}
\end{align*}
\]

The data presented and that in the literature do indicate the reaction depends upon the polarization of the carbon-halogen bond in the acid halide and the nucleophilic character of the ketene α-carbon.

That the addition of acid halides to ketenes involves an ionic process is supported by the finding of Sorm and coworkers that Lewis acids catalyze the reaction. Also, it was found that the use of liquid sulfur dioxide as the reaction solvent doubled the yields of the isolated 3-ketoacid esters as compared to chloroform as the solvent (22).
Some evidence which could indicate the presence of an acyl cation intermediate is Sorm's report that trichloroacetyl chloride in the presence of excess ketene produced X and XI (21, 22). Reaction of an initial 3-ketoacyl cation with the excess ketene could produce X. Rearrangement of the resulting acyl cation, rather than reaction with chloride ion to give X, would produce XI.

\[
\begin{align*}
\text{CH}_2=\text{C}=\text{O} + \text{CCl}_3\text{C}= \rightarrow & \text{CCl}_3\text{CH}_2 \text{O}^+ \text{Cl}^- \\
\text{CCl}_3\text{C}= \rightarrow & \text{CCl}_3\text{CH}_2 \text{CCH}_2 \text{C}^+ \text{Cl}^- \\
& \text{or} \\
\text{X} & \text{CCl}_3 \text{XI}
\end{align*}
\]

Further support for an acyl cation attacking species can be drawn by analogy from the reaction of nitroly chloride with ketene to produce nitroacetyl chloride. The attacking species is the classic electrophile, the nitronium ion (26).

\[
\begin{align*}
\text{NO}_2\text{Cl} & \rightarrow \text{NO}_2^+ \text{Cl}^- \\
\text{NO}_2^+ + \text{CH}_2\text{C}=\text{O} & \rightarrow \text{NO}_2\text{CH}_2\text{C}=\text{O}
\end{align*}
\]
The experimental data presented have shown the reactivity order of ketenes toward acid chlorides is dimethylketene > ketene > diphenylketene. The nucleophilic character of the α-carbon in the ketenes decreases in the same order. Thus, in reaction mechanisms involving either a discrete acylation or a complex with charge separation, the ketene reactivity would analogously decrease.

The polarization of the carbon-halogen bond, C-X, in a series of acid chlorides parallels the inductive effects of the substituent attached to the carbonyl as does the pKa of the parent acid. Therefore the reactivity of a series of acid chlorides toward a ketene by a mechanism involving C-Cl bond cleavage should parallel the pKas of the parent acids. This has been found to be true for dimethylketene and ketene.

That dichloroacetyl bromide reacts more vigorously with dimethylketene than dichloroacetyl chloride indicates the ease of C-X cleavage is a factor in reactivity. Thus in acylation of ketenes by acid halides, as in the acylation of alkenes, the reaction depends on the nucleophilicity of the α-carbon in the ketene, the nucleophilic partner, and the degree of polarization, or ease of cleavage, of the C-X bond in the acid halide.

In summary, the addition of acid halides to ketenes has been shown to be of limited synthetic value and less than general in that the scope of the reaction is limited by (a)
reactivity of the ketenes; (b) reactivity of the acid halides; and (c) to ketenes which can be isolated. Acid chlorides were shown to parallel their parent acid pKa's in reactivity toward dimethylketene. Dimethylketene was found to be more reactive than either diphenylketene or ketene. The reactivity order of dimethylketene > ketene > diphenylketene was established.

The data presented here and in the literature are interpreted to show the reaction is an ionic process involving an attack of the acid halide on the ketene olefinic double bond. The addition is dependent upon the polarity of the carbon-halogen bond in the acid halide and the degree of nucleophilicity of the ketene α-carbon.
BIBLIOGRAPHY


PART II

THE CYCLOADDITION OF KETENES

TO CARBONYL COMPOUNDS
Chapter I

Introduction

The carbon-carbon double bond of stable, isolable ketenes can be caused to react with the carbon-oxygen double bonds of carbonyl compounds to produce 2-oxetanones, or $\beta$-lactones (26).

\[
\begin{align*}
\text{R} & \text{C=O} + \text{R} \text{C=O} \rightarrow \text{R} \text{O} \text{R} \text{O} \\
\end{align*}
\]

Staudinger and coworkers accomplished the cycloaddition of diphenylketene to various carbonyl compounds during their early investigations of ketene reactions (28). However, the high temperatures required to effect the cycloadditions decarboxylated the $\beta$-lactones produced, and only the resulting olefins were isolated (13, p. 806).

\[
\begin{align*}
\text{R} \text{O} \text{R} \text{O} \rightarrow \Delta & \text{R} \text{O} + \text{CO}_2 \\
\end{align*}
\]

Since the high temperatures required for cycloadditions polymerized aldoketenes and lower ketoketenes, early investigations were limited to diphenylketene (31).
Later the cycloaddition of ketene to aldehydes was found to proceed smoothly in ether in the presence of mild Friedel-Crafts type catalysts (22). Ketones, however, required much stronger catalysts and more vigorous conditions to react with ketene (34).

\[
\text{CH}_2\text{C}=\text{O} + \text{RCHO} \xrightarrow{\text{catalyst}} \text{R(C}_2\text{H}_5\text{O}_2\text{CH})_2
\]

The cycloadditions of ketene to carbonyl compounds and suitable catalysts for the reactions have subsequently been extensively investigated. This work has been reviewed by Zaugg (34) and Hagemeyer (17), and the compounds which have been used as catalysts have been tabulated by Muller and Hamer (26).

More recently, the cycloaddition of low-molecular-weight dialkylketenes to aldehydes employing Lewis acid catalysts has been described in the patent literature (19). For example, diethylketene was reported to react with propionaldehyde to produce 3,3,4-triethyl-2-oxetanone.

\[
\text{R} = \text{C}_2\text{H}_5
\]
However, ketenes which are isolable and stable are far fewer in number than those which can only be trapped by in situ reactions. The most common in situ method of preparing ketenes has been the reaction of an acid halide having an α-hydrogen with a tertiary amine (23, p. 1168).

\[
\begin{align*}
(R)_2CH^\text{O}X + (R)_3N & \rightarrow (R)_2C=\text{C}=O + (R)_3\text{NHX}
\end{align*}
\]

In ketene-carbonyl cycloadditions by this method, Lewis acid catalysts cannot be employed as with isolable ketenes since such catalysts would be neutralized by the tertiary amine. Therefore, only those reactions requiring no Lewis acid catalyst are possible by in situ dehydrohalogenation.

Bormann and Wegler have recently reported that in situ cycloadditions by dehydrohalogenation are possible when the carbonyl compound is activated by electronegative substituents on the α-carbon (2). Thus the in situ cycloadditions of several ketenes to chloral were accomplished with substituted acetyl chlorides and triethylamine.

\[
\begin{align*}
(R)_2CH_3CCl + CCl_3CHO & \rightarrow (C_2H_5)_3\text{N} \quad \text{CCl}_3\text{O}
\end{align*}
\]

A report since the present investigation was initiated has revealed that the dehydrohalogenation of dichloroaacetyl
chloride in the presence of simple aldehydes results in dichloroketene adducts (4).

\[
\text{CHCl}_2\text{Cl} + R\text{CHO} \xrightarrow{(\text{C}_2\text{H}_5)_3\text{N}} \text{R} \begin{array}{c} \text{O} \\ \text{Cl} \\ \text{H} \end{array} \]

\(\varphi\)-Lactones were also obtained from dichloroketene and \(\alpha\)-ketoacid esters, but simple ketones, such as acetone, cyclohexanone and acetophenone did not react with dichloroketene.

England and Krespan were able to trap difluoroketene with acetone by dehalogenating bromodifluoroacetyl chloride with zinc in acetone (12). However, the dehalogenation of \(\alpha\)-haloacyl halides has not been further investigated as an in situ method of ketene-carbonyl cycloadditions.

\[
\text{CBrF}_2\text{Cl} + \text{(CH}_3\text{)}_2\text{C}=\text{O} \xrightarrow{\text{Zn}} \text{CH}_3\begin{array}{c} \text{O} \\ \text{F} \end{array}
\]

In the reports cited above and those found in reviews by Lacey (23), Zaugg (34), Muller and Hamer (26), and Etienne and Fisher (13), aldoketene-carbonyl cycloadditions have been very rare. Also, in the few cases of aldoketene and unsymmetrically substituted ketoketene cycloadditions to unsymmetrically
substituted carbonyl compounds, i.e., where geometrical isomers of the 2-oxetanones are possible, no description of the stereochemical course of the reaction, excluding optical isomerism, has been given (2, 3, 19).

The geometrical isomerism of the products is of interest because such data often indicate the reaction mechanism (15). Aldoketene-imine cycloadditions, shown to proceed via dipolar intermediates, stereospecifically produce the trans isomers of 2-azetidinones (24).

In contrast, the cycloaddition of aldoketenes to olefins, a process shown to be near concerted (1, 7, 8, 20, 21), stereospecifically produces the cis or endo isomers of the cyclobutanones (5, 6, 10).
Since the Lewis acid catalysis of ketene-carbonyl cycloadditions is a well documented fact, the reaction has been assumed to be an ionic, two-stepped process. Other evidences such as 1:2 and 2:1 adducts have been sited as indicative of the occurrence of dipolar intermediates (2). Therefore, if ketene-carbonyl cycloadditions do proceed via a dipolar intermediate, similar to ketene-imine cycloadditions, stereospecificity or stereoselectivity of the same type might be exhibited in the products as formed.

In summary, the literature on ketene-carbonyl cycloadditions reveals the following: (a) Essentially no work has been done with aldoketenes. (b) No geometrical isomerism has been reported for 2-oxetanones arising from unsymmetrically substituted carbonyl compounds. (c) With the exception of England and Krespan's work, dehalogenation has not been explored as an in situ method of effecting ketene-carbonyl cycloadditions. (d) Isolable ketenes require either Lewis acid catalysts or elevated temperatures or both to participate in carbonyl cycloadditions.
With these observations, an investigation of the general reaction was approached in the following manner: *In situ* cycloaddition of several aldoketenes to chloral by both dehydrohalogenation and dehalogenation; determination and comparison of the isomer distributions of the products in both methods; investigation and comparison of the synthetic aspects of the two methods, with special emphasis on *in situ* dehalogenation. Aldoketenes were chosen for the study because their cycloadditions to carbonyl compounds have largely been unreported and because aldoketene-aldehyde adducts could be easily identified as the *cis* or *trans* isomers on the basis of the nmr coupling constants of the methinyl protons (9).

\[
\begin{align*}
\text{cis, } J &= 6\text{cps} \\
\text{trans, } J &= 3\text{cps}
\end{align*}
\]

Chloral was chosen as the trapping agent because of its enhanced reactivity and the steric bulk presented by the trichloromethyl group.
Chapter II

Experimental

Nuclear magnetic resonance (nmr) spectra were recorded on a Jeolco Minimar 60 mHz or Jeolco NMR PS-100 100 mHz spectrometer. Spectra were obtained from carbon tetrachloride or chloroform-d solutions with approximately 1% tetramethylsilane as an internal standard, \( \delta = 0.00 \) ppm. Spectra were recorded at room temperature.

Infrared (ir) spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer. Spectra were obtained using neat samples between sodium chloride discs or as approximately 5% solutions in carbon tetrachloride in 0.1 mm fixed thickness sodium chloride cells. Spectra of reaction solutions were recorded in the carbonyl region of the spectrum by placing the solution in the fixed thickness cell.

Mass spectra were obtained with a Hitachi RMU-6E mass spectrometer.

An F and N Scientific Model 700 was used for analytical gas chromatography and an Aerograph 90A was used for small scale preparative purposes. In both instruments, thermal conductivity detection systems were used. Columns of 4, 6 and 8 ft. by 0.25 in. packed with 10% SE 30 on Chromosorb W (DMCS) 60/80 mesh were used on both instruments.
Elemental analyses were obtained from the Analytical Services Section, Department of Chemistry, North Texas State University and C. F. Geiger and Associates, Ontario, California.

Preparation of solvents and reagents. All solvents were reagent grade, commercially available chemicals. All were distilled from appropriate drying agents such as sodium shavings, calcium hydride or lithium aluminium hydride and stored over Molecular Sieves, 4A, under dry nitrogen.

The following reagents were commercially available: Propionyl chloride, trichloroacetyl chloride, triethylamine, chloral, acetone, 2-butanone, cyclohexanone, phenylacetyl chloride, 2-bromo-2-methylpropanoyl bromide, propionaldehyde and the acids required in the preparation of the following acid halides.

Diphenylacetyl chloride, 2-phenylbutanoyl chloride, 2-chloro-2-phenylethanoyl chloride, dichloroacetyl chloride, chloroacetyl chloride, 2-bromopropanoyl chloride and 2-bromo-3-methylbutanoyl chloride were prepared by standard literature preparations employing common halogenating agents. The acid chlorides were redistilled immediately prior to use.

The isolable ketenes were prepared by standard procedures found in the literature. Diphenyl- (30), and phenylethylketenes (11) were prepared by dehydrochlorination of diphenylacetyl and 2-phenylbutanoyl chlorides with triethylamine. The ketenes were isolated by distillation at reduced pressures.
Dimethylketene was prepared by pyrolysis of the commercially available dimer, tetramethyl-1,3-cyclobutadione (18).

Zinc amalgam was prepared by the following procedure (12). Granular zinc (15 g, 20 mesh) was rinsed in 75 ml of 5% aqueous hydrochloric acid containing 0.1 g mercuric chloride per 50 ml until the surface was bright. The zinc was separated by filtration, washed with distilled water and with acetone, and dried with a stream of nitrogen. The zinc amalgam was transferred to the reaction flask under nitrogen and covered with ether.

Chloral was vacuum distilled, bp 40° at 80 mm, and stored under nitrogen in brown glass bottles with septum caps at 0-5°. Portions were removed with a 25 ml syringe as needed. Other aldehydes and ketones were distilled and stored in the same manner.

**Determination of isomer distributions.** At various intervals during the additions in both dehydrohalogenation and dehalogenation reactions, 1 ml aliquots were removed and centrifuged. Samples of the supernatant were then analyzed by vpc. Retention times were compared to previously characterized samples of the compounds in the reaction. Isomer distributions were determined as the ratio of peak areas, calculated by peak height times width at one half peak height. An alternate method was removal of a sample after the reactions were complete, centrifugation, addition of tetramethysilane to the supernatant,
and integration of the methinyl region in the nmr spectrum. The isomer ratios were taken as the ratio of the integrations of the doublets having the characteristic cis and trans coupling constants. The two methods were compared on an artificial mixture of cis- and trans-3-methyl-4-trichloromethyl-2-oxetanone, I, having cis/-trans-I = 1.10. The vpc method showed cis/-trans-I = 1.06, and the nmr method showed cis/-trans-I = 1.12.

Cycloaddition of methylketene to chloral by in situ dehydrochlorination; 3-methyl-4-trichloromethyl-2-oxetanone, I. Triethylamine, 32.4 ml (230 mmol), in 75 ml of ether was added to a vigorously stirred solution of propionyl chloride, 20.0 ml (230 mmol), and chloral, 20.0 ml (204 mmol), in 300 ml of ether at room temperature. Filtration of the reaction mixture after four hours yielded a theoretical amount of salt. Concentration of the filtrate and distillation of the residue yielded a crude mixture of cis- and trans-I, 43%, based on chloral. Fractional distillation gave three fractions, 51-40, 54-50, and 560 at 0.2 mm. The first two fractions were shown to be mixtures of cis- and trans-I; ir, 1870 cm⁻¹ (C=O); nmr (CDCl₃), cis-I, 5.08 (d, J = 6.8 cps), 4.2 (m) and 1.55 (d); trans-I 4.77 (d, J = 3.2 cps), 3.81 (m) and 1.55 (d). Fraction three was found to be pure cis-I; nmr (CCl₄), 4.98 (d, J = 6.8 cps, H), 4.08 (m, 1H) and 1.53 (d, 3H). Spin decoupling of the methyl resonance at 1.53 reduced the quintet at 4.08 to a
doublet, $J = 6.8$ ops. Spin decoupling of the quintet reduced the methyl doublet to a singlet.

Anal. Calcd. for C$_5$H$_5$Cl$_3$O$_2$: C, 29.52; H, 2.48. Found: C, 29.66; H, 2.46. The cis-/trans-I in the reaction was 1.39 as determined by vpc.

The dehydrochlorination of propionyl chloride in the presence of chloral was also carried out in hexane, tetrahydrofuran and acetonitrile with approximately the same yields and isomer distributions of I.

**Cycloaddition of methylketene to chloral by in situ dehalogenation: 3-methyl-4-trichloromethyl-2-oxetanone, I.**

A solution of 2-bromopropanoyl chloride, 10.0 ml (98.5 mmol), in 25 ml ether was added dropwise to rapidly stirred zinc amalgam 12 g, in 150 ml ether containing chloral, 15.0 ml (153 mmol). The reaction temperature was maintained below the boiling point of ether by cooling the reaction flask with a water bath. Filtration of the reaction mixture after four hours showed a theoretical amount of zinc had been consumed. The filtrate was concentrated and extracted with hexane. Distillation of the concentrated hexane extracts produced I in 95% yield. The isomer distribution in the reaction mixture during the reaction was 2.1 as determined by vpc.

**Cycloaddition of chloroketene to chloral by in situ dehydrohalogenation; 3-chloro-4-trichloromethyl-2-oxetanone, II.**
Triethylamine, 18.7 ml (132 mmol), in 50 ml hexane was slowly added to a rapidly stirred solution of chloroacetyl chloride, 10.0 ml (132 mmol), and chloral, 15.0 ml (153 mmol), in 150 ml hexane at room temperature. After the addition was complete, stirring was continued two hours. Filtration yielded a theoretical amount of salt. Concentration of the filtrate and distillation of the residue yielded (40%) a mixture of cis- and trans-II; ir 1870 cm⁻¹ (C=O); nmr (CDCl₃), cis-II, pair of doublets centered at 5.58 and 5.18$\delta$(J = 6.0 cps); trans-II, pair of doublets centered at 5.25 and 5.04$\delta$(J = 3.0 cps).

Fractional distillation at 0.1 mm gave trans-II, bp 56-80°, several fractions containing both isomers and cis-II, bp 78-80°, nmr (CCl₄), trans-II, δ5.44 (d, J = 3.0 cps, 1H), 5.17 (d, J = 6.0 cps, 1H).

Anal. Calcd. for C₇H₅Cl₂O₂: C, 21.46; H, 0.90. Found: C, 21.48; H, 1.02.

The cis-/trans-II in the reaction mixture was 1.64 as determined by vpc.

The dehalogenation of chloroacetyl chloride in the presence of chloral was also carried out in ether, tetrahydrofuran and acetone and produced approximately the same isomer ratio. The yield in acetone was lower, while the ethers produced a slightly higher yield than hexane.
10 ml ether was added to zinc amalgam, 10 g, in 50 ml ether containing chloral, 6.0 ml (61 mmol), with rapid stirring and warming with a water bath. IR spectra of the reaction solution showed only a very low concentration of II and strong C=O absorption at 1785 cm$^{-1}$. Filtration showed less than a theoretical amount of zinc had been consumed. The filtrate was concentrated and extracted with hexane. The hexane extract was concentrated in vacuo and the residue distilled. Yield 4.1 g, 60%, bp 38-9° at 0.15 mm; ir 1785 cm$^{-1}$(C=O) and 1650 cm$^{-1}$(C=C); nmr (CDCl$_3$), 7.56(s, 1H) and 6.20(s, 1H).

Anal. Calcd. for C$_5$H$_2$Cl$_4$O$_2$: C, 21.5; H, 0.90. Found: C, 21.53; H, 0.97. Calculated molecular weight 222. Found by mass spectrum, 222. These data are consistent with the structure of VIII, 1,2-dichlorovinyl dichloroacetate.

\[ \text{CHCl}_2\text{C}=\text{O}-\text{CCl=CHCl} \]

VIII

**Cycloaddition of isopropylketene to chloral by in situ dehalogenation; 3(2-propyl)-4-trichloromethyl-2-oxetanone, III.**

A solution of 2-bromo-3-methylbutanoyl chloride, 25.0 ml (215 mmol), in 50 ml ether, were added dropwise to rapidly stirred zinc amalgam, 20.0 g, in 300 ml ether containing chloral, 30 ml (306 mmol). Filtration after four hours showed a theoretical amount of zinc had been consumed. The filtrate
was concentrated and extracted with hexane twice. The hexane was removed from the extracts in vacuo and the residue distilled yielding 25% III. Separation of cis- and trans-III and other components were not possible by fractional distillation. Cis-III was obtained by preparative vpc of the crude residue from the hexane extracts; ir, 1860 cm\(^{-1}\) (C=O); nmr (CDCl\(_3\)), \(\delta 5.30\) (d, J = 6.0 cps, 1H), 3.95 (m, 1H), 2.73 (m, 1H), 1.27 (t, 6H).

Anal. Calcd. for C\(_7\)H\(_9\)Cl\(_3\)O\(_2\): C, 36.3; H, 3.92. Found: C, 36.5; H, 3.84.

Trans-III was separated from the other components by elution from a 18 X 300 mm silica gel column with 70/30 cyclohexane/benzene; nmr (CDCl\(_3\)), \(\delta 5.0\) (d, J = 3.5 cps, 1H), 3.72 (m, 1H), 2.37 (m, 1H), 1.25 (d, 6H).

The isomer distribution in the reaction mixture was 0.9 as determined by vpc.

Cycloaddition of phenoxyketene to chloral; 3-phenoxy-4-trichloro-2-oxetanone, IV. Triethylamine, 15.5 ml (110 mmol), in 25 ml tetrahydrofuran was added dropwise to a rapidly stirred solution of phenoxyacetyl chloride, 15.0 ml (110 mmol), and chloral, 15.0 ml (153 mmol), in 200 ml tetrahydrofuran at room temperature. After two hours, filtration yielded a theoretical amount of salt. Distillation of the concentrated filtrate produced two main fractions of IV (61%), bp 140\(^\circ\) and 157\(^\circ\) at 0.2 mm. The second fraction solidified and was purified by sublimation at 70\(^\circ\) and 0.05 mm, mp 70-72\(^\circ\); cis-IV,
1870 cm\(^{-1}\) (C=O), nmr (CDCl\(_3\)), \(\delta\) 7.2 (m, 5H), 5.62 (d, \(J = 6.0\) cps, 1H), 5.10 (d, \(J = 6.0\) cps, 1H). **Trans-IV**, bp 140° at 0.2 mm, literature bp 128 at 0.1 mm (2); nmr (CDCl\(_3\)), \(\delta\) 7.2 (m, 5H), 5.62 (d, \(J = 3.0\) cps, 1H), and 5.17 (d, \(J = 3.0\) cps, 1H).

The isomer distribution was determined by integration of the methinyl region of the nmr spectrum of the reaction solution. In these samples the down field doublets of the two isomers were used since the up field doublets of the isomers were superimposed. **Cis-/ trans-IV = 1.7.**

**Cycloaddition of dimethylketene to chloral by in situ dehalogenation:** 3,3-dimethyl-4-trichloromethyl-2-oxetanone, V. 2-Bromo-2-methylpropanoyl bromide, 10.0 ml (83 mmol), in 20 ml ether was added to rapidly stirred zinc amalgam, 15 g, in 200 ml ether containing chloral, 15 ml (153 mmol), at room temperature. Filtration of the reaction mixture after eight hours showed a theoretical amount of zinc had reacted. The filtrate was concentrated and extracted with hexane. The hexane extracts were concentrated to yield crystalline V, 60%. V was further purified by sublimation at 45° and 0.1 mm; mp 62°-3°, literature mp 65° (28); nmr (CDCl\(_3\)), \(\delta\) 4.74 (s, 1H), 1.60 (d, 6H).

**Cycloaddition of dimethylketene to chloral by in situ dehydrochlorination.** Triethylamine, 13.5 ml (95.5 mmol), in 25 ml tetrahydrofuran was added dropwise to a rapidly
stirred solution of chloral, 15 ml (153 mmol), and isobutyryl chloride, 10.0 ml (95.5 mmol), in 200 ml tetrahydrofuran at room temperature. The ir spectrum of the reaction solution indicated V was formed. The yield of V was estimated to be 15\% by comparison of the gas chromatogram of the reaction solution to that of a standard solution of V. Isolation of the product was complicated by the presence of tetramethyl-1,3-cyclobutadione, dimethylketene dimer.

**Cycloaddition of dimethylketene to chloral.** To a flask containing 195 mmol dimethylketene in 50 ml ether was added 10.0 ml (102 mmol) chloral. The resulting solution was transferred by syringe to two septum bottles, one with 2 g zinc amalgam and one empty. After one hour, both solutions contained V as evidenced by vpc analysis. During the next several hours the concentration of V, as estimated by comparison of vpc peak areas of sample and standard solutions of V, were 10 and 65\% for the control and zinc amalgam sample respectively: ir both solutions, 1850 cm\(^{-1}\) (C=O).

**Cycloaddition of dimethylketene to propionaldehyde.** A solution of dimethylketene, 16.4 g (230 mmol), and propionaldehyde (350 mmol) in 100 ml ether was prepared. This solution was transferred to three septum bottles: (a) an empty bottle designated as a control, (b) a bottle containing 1.0 g anhydrous zinc chloride, and (c) a bottle containing 4.0 g zinc amalgam.
The bottles were vigorously shaken. After six hours all three samples showed $\beta$-lactone carbonyl absorption, 1840 cm$^{-1}$, in the ir spectra. Analysis of the solutions by vpc indicated the concentration of product in (c) to be twice that in (a) and 1.4 times that in (b). Concentration of solution (c) and preparative vpc yielded 3,3-dimethyl-4-ethyl-2-oxetanone; ir, 1840 cm$^{-1}$ (C=O); nmr (CDCl$_3$), $\delta$ 4.23 (t, 1H), 1.8 (m, 2H), 1.45 (s, 3H), 1.28 (s, 3H), 1.05 (t, 3H); literature reference (19).

Cycloaddition of dichloroketene to acetone by in situ dehalogenation; 3,3-dichloro-4,4-dimethyl-2-oxetanone, VI.

Trichloroacetyl chloride, 25.0 ml (228 mmol), in 50 ml ether was added dropwise to rapidly stirred zinc amalgam, 18 g, in 100 ml acetone and 500 ml ether. The reaction temperature was maintained at 27° with a water bath. Filtration after four hours showed 86% of a theoretical amount of zinc had been consumed. The filtrate was concentrated and extracted with hexane. The hexane was removed from the extract in vacuo. Distillation of the residue yielded 30% VI; bp 34° at 0.5 mm; mp 24-5°; ir, 1875 cm$^{-1}$ (C=O); nmr (CCl$_4$), 1.79$\delta$(s).

Anal. Calcd. for C$_5$H$_6$Cl$_2$O$_2$: C, 35.5; H, 3.58. Found: C, 35.7; H, 3.47.

Cycloaddition of dichloroketene to cyclohexanone by in situ dehalogenation; 3,3-dichloro-1-oxaspiro 3,5 nonan-2-one, VII.
Trichloroacetyl chloride, 20.0 ml (182 mmol), in 50 ml ether was added dropwise to rapidly stirred zinc amalgam, 15 g, in 200 ml ether containing 25.0 ml cyclohexanone. The reaction temperature was maintained at 30° with a water bath. Filtration after six hours showed 90% theoretical consumption of zinc. The filtrate was concentrated and extracted with hexane. Removal of the hexane and distillation of the residue afforded a 51% yield of VII; bp 62° at 0.2 mm; ir 1850 cm⁻¹ (C=O); nmr (CDCl₃), δ1.8, unresolved multiplet.

Anal. Calcd. for C₇H₁₀Cl₂O₂: C, 45.9; H, 4.82. Found: C, 45.7; H, 5.17.

Attempted pyrolysis of cis-I. A sample of cis-I was placed in a flask and heated at 150° under nitrogen for six hours. Cis-I, 90%, was recovered by vacuum distillation as evidenced by its ir and nmr.

Attempted pyrolysis of trans-II. A sample of trans-II was heated at 160° for twelve hours. Trans-II, 94%, was recovered by vacuum distillation as evidenced by ir and nmr spectra.

Pyrolysis of VI. A sample of VI was heated at 150° for two hours. Distillation yielded 50% 1,1-dichloro-2-methylpropene, bp 106-7°, literature bp 108-110° (14).
Chapter III

Results and Discussion

In the few literature reports where ketene-carbonyl cycloadditions could give rise to geometrical isomers, the stereochemical course of the cycloadditions has not been reported (2, 3, 19). Borrmann and Wegler, in the only report of aldoketene-carbonyl cycloadditions, described the cycloaddition of phenoxy- and ring-substituted phenoxyketenes to chloral but did not describe the stereochemistry of the products (2, 3).

The cycloaddition of aldoketenes to chloral produces cis- and trans-4-trichloromethyl-2-oxetanones.

\[
\begin{align*}
R = & \text{I, CH}_3; & \text{II, Cl; } & \text{III, } \text{iPr; } & \text{IV, } \text{O} \\
\end{align*}
\]

The aldoketenes were generated in situ by the dehydrochlorination of the appropriately substituted acyl chlorides (23, p. 1168).
RCH₂\text{Cl} + (\text{C}_2\text{H}_5)_3\text{N} \rightarrow \text{[RCH=CH]} + (\text{C}_2\text{H}_5)_3\text{NHCl}

and/or by dehalogenation of appropriately substituted \text{\alpha}-haloacyl halides with zinc amalgam (23, p. 1165).

\[
\begin{align*}
\text{RCHX}_{\text{ether}} & \xrightarrow{\text{Zn}} \text{[RCH=C=O]} & + & \text{ZnX}_2
\end{align*}
\]

Cycloaddition of carbonyl compounds and ketenes generated by \textit{in situ} dehydrohalogenation has recently been investigated by Borrmann and Wegler (2,4), but cycloadditions of carbonyl compounds and ketenes produced \textit{in situ} by dehalogenation has received little attention (12).

As England and Krespan found in the generation of difluoroketene by \textit{in situ} dehalogenation, the \text{\alpha}-bromoacyl chloride is the preferred acid halide (12; 23, p. 1165). 2-Bromopropanoyl chloride consistently dehalogenated with greater ease, as evidenced by the amount of zinc consumed, than did the bromo-bromide, the chloro-bromide, or the chloro-chloride.

The isomeric \text{\beta}-lactones were isolated and separated by fractional distillation, preparative vpc, or column chromatography and identified by their ir and nmr spectra.
Configurational assignments were made on the basis of the nmr coupling constants of the methinyl protons (9, 16).

\[
\begin{align*}
J_{ab\text{cis}} &= 6 \text{ cps} \\
J_{ab\text{trans}} &= 3 \text{ cps}
\end{align*}
\]

The doublet for $H_a$ appears down field from the resonance of $H_b$ by 25-75 cps (16).

The isomer distributions were determined as ratios of integrated peak areas on gas chromatograms of the reaction solutions with the exception of the phenoxyketene-chloral system. The ratio, cis-/ trans-IV, was obtained by nmr integration of the methinyl region.

The vpc and nmr methods were compared by making an artificial mixture of cis- and trans-3-methyl-2-oxetanone, I. The ratio, cis-/ trans-I, in the mixture was 1.10 by weight. An average of several integrations of the cis and trans methinyl doublets in the nmr spectrum (30% in CDCl$_3$) of the mixture yielded cis-/ trans-I = 1.12. The average integration of the peak areas in several chromatograms from the nmr solution yielded cis-/ trans-I = 1.06. The experimentally determined distributions for compounds I-IV are summarized in Table I.
Table I
Aldoketene-Chloral Cycloadditions

![Image of cycloaddition reaction]

<table>
<thead>
<tr>
<th>R</th>
<th>Method⁵</th>
<th>cis/trans</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>I CH₃⁻</td>
<td>DHX</td>
<td>1.4</td>
<td>43%</td>
</tr>
<tr>
<td>I CH₃⁻</td>
<td>DX</td>
<td>1.4-2.0</td>
<td>95%</td>
</tr>
<tr>
<td>II Cl⁻</td>
<td>DHX</td>
<td>1.6</td>
<td>40%</td>
</tr>
<tr>
<td>IV Ph⁻</td>
<td>DHX</td>
<td>1.7</td>
<td>61%</td>
</tr>
<tr>
<td>III i-Pr⁻</td>
<td>DX⁻</td>
<td>0.9</td>
<td>25%</td>
</tr>
</tbody>
</table>

⁵ DHX, dehydrohalogenation; DX, dehalogenation.

Increased yield in the synthesis of I by dehalogenation as opposed to dehydrochlorination may be seen in Table I.

To further explore the enhanced reactivity of ketenes generated

\[
\begin{align*}
\text{CCl}_3\text{CCl} + (\text{CH}_3)_2\text{C}=\text{O} & \xrightarrow{\text{Zn, ether}} \text{CH}_3\text{C}\text{Cl}\text{C}=\text{O}_\text{VI} \\
\text{CCl}_3\text{CCl} + \text{C}_8\text{H}_8\text{C}=\text{O} & \xrightarrow{\text{Zn, ether}} \text{C}_8\text{H}_8\text{C}=\text{O}_\text{VII}
\end{align*}
\]
in situ by dehalogenation, dehalogenations of trichloroacetyl chloride in the presence of acetone and cyclohexanone were investigated and found to produce VI and VII.

Borrmann and Wegler reported that dichloroketene generated in the presence of these ketones by dehydrohalogenation did not produce β-lactones (3). Therefore, by dehalogenation in situ, a heretofore unknown series of 4,4-dialkyl-2-oxetanones can be synthesized.

As a comparison of the two methods, dimethylketene, when prepared by in situ dehydrochlorination of isobutyryl chloride with triethylamine in the presence of chloral, yielded 15% V. Debromination of 2-bromo-2-methylpropanoyl bromide with zinc amalgam in the presence of chloral produced 60% V.

\[
\begin{align*}
(CH_3)_2CHCCl + CCl_3CHO & \xrightarrow{(C_2H_5)_3N} CCl_3CHCCl + CCl_3CHO \quad 15\% \\
(CH_3)_2CBrCCl + CCl_3CHO & \xrightarrow{Zn, ether} CCl_3CHCCl + CCl_3CHO \quad 60\% V
\end{align*}
\]

When dimethylketene was prepared by pyrolysis of its dimer, tetramethyl-1,3-cyclobutadione, and combined with chloral in ether, V was produced in 10% yield. An identical
sample containing zinc amalgam yielded 65% V. Oshe and coworkers have reported V is obtained in 65% yield when the cycloaddition is catalyzed by boron trifluoride etherate (28).

Dimethylketene was also shown to be more reactive toward propionaldehyde when zinc amalgam was included in the reaction flask; the yield of 3,3-dimethyl-4-ethyl-2-oxetanone was doubled.

In an attempt to produce chloroketene and effect the in situ cycloaddition to chloral by dehalogenation, dichloroacetyl chloride and chloral were treated in the usual manner with zinc amalgam. The product isolated, however, was concluded to be 1,2-dichlorovinyl dichloroacetate, VIII, from the spectral elemental analyses. England and Krespan reported a similar vinyl ester was produced in the dehalogenation of bromodifluoroacetyl chloride (12).

\[
\text{CHCl}_2\text{C}^\text{O}\cdot\text{CCl}^\text{=CHCl} \\
\text{VIII}
\]

It was hoped that the cycloaddition of phenylethylketene, an isolable ketene, and chloral could be effected so that the isomer distribution could be compared to those of the in situ systems. However, phenylethylketene exhibited very little reactivity toward chloral—whether combined in a
solution and heated, catalyzed by anhydrous zinc chloride, or produced in situ by dehydrochlorination in a variety of solvents. The only indication of $\beta$-lactone was found in a reaction solution which contained zinc amalgam. A weak C=O absorption appeared at 1850 cm$^{-1}$ and concentrated samples showed a small singlet in the methinyl region of the nmr spectrum. However, the isolation of the $\beta$-lactone was not possible.

Phenylketene also showed very little reactivity toward chloral when produced by dehydrohalogenation in tetrahydrofuran, ether, hexane and acetonitrile. Although very weak $\beta$-lactone C=O absorptions were seen in ir spectra of reaction solutions, the various methods of isolation failed to yield the $\beta$-lactone.

The enhancement of reactivity in dehalogenation systems versus dehydrohalogenation is probably due to activation of the carbonyl compound since the reactivities of ketenes toward olefin cycloadditions show no increase over the corresponding dehydrohalogenation. Although there is an enhancement of reactivity, the reactivities of dichloroketene and methylketene differ markedly. When methylketene was produced in situ by dehydrohalogenation, no evidence of cycloaddition to benzaldehyde, propionaldehyde, acetone, 2-butanone, or cyclohexanone could be found. It is probable that propionaldehyde trimerized under the strongly acidic reaction conditions.
$\beta$-Lactones normally eliminate carbon dioxide and produce olefins when heated (13, p. 806). However, when heated at $160^\circ$ for six to twelve hours, I and II were recovered unaltered. The unusual thermal stability of 4-trichloromethyl-2-oxetanones has been reported by Ohse and coworkers for 3,3-dimethyl-4-trichloromethyl-2-oxetanone, V (28). When heated, 3,3-dichloro-4,4-dimethyl-2-oxetanone, VI, decarboxylated in the expected manner to produce 1,1-dichloro-2-methylpropene.

There is evidence that in the transition state of the elimination the carbon in the 4-position of the 2-oxetanone ring is positive (27). A trichloromethyl group in the 4-position would destabilize this transition state compared to alkyl groups. The result is remarkable thermal stability for 4-trichloromethyl-2-oxetanones relative to 4-alkyl-2-oxetanones.

When the two extremes of possible cycloaddition mechanisms, i.e., a near concerted process and a two-step process with a dipolar intermediate, are considered, the data for ketene-carbonyl cycloadditions strongly suggest a near concerted process.

$$\begin{align*}
\text{(CH}_3\text{)}_2\text{C=CCl}_2 & \xrightarrow{\Delta} (\text{CH}_3\text{)}_2\text{C=CCl}_2 + \text{CO}_2
\end{align*}$$
Aldoketene-olefin cycloadditions are near concerted processes and stereospecifically produce cis or endo cyclobutanones (5, 6, 10).

\[
RCH=\text{C}=\text{O} \quad + \quad \text{C}_{5}\text{H}_{5} \quad \rightarrow \quad \text{endo}
\]

In contrast aldoketene-imine cycloadditions, shown by Luche and Kagan to occur via a dipolar intermediate, stereospecifically produce trans-2-azetidinones (24).

\[
RCH=\text{C}=\text{O} \quad + \quad \text{N:C}=\text{H} \quad \rightarrow \quad \text{trans}
\]

Ketene-carbonyl cycloadditions have been assumed to be ionic processes with dipolar intermediates largely on the basis of Lewis acid catalysis of the reaction (15). Other evidences in support of this assumption are the isolation of 1:2 and 2:1 adducts (2). However, in cases where 1,4 cycloaddition would be expected if a dipolar intermediate were present, the products observed have been shown to be the
result of 1,2-cycloadditions. McCain and Marcus have shown that acrolein and ketene catalyzed by BP₂ produce 4-vinyl-2-oxetanone rather than a 1,4 adduct (25), and Young has observed that the isolated product from addition of ketene to acetyl oxide arises from rearrangement of the 3-oxetone produced initially by 1,2 cycloaddition rather than via a 1,4 cycloaddition (33).

In the cycloaddition of aldehydes to chloral, the formation of the new bonds must either occur simultaneously or in rapid succession since the production of the sterically hindered cis isomer predominates. As in the cycloaddition of aldehydes to imines, a long-lived dipolar intermediate would be expected to produce the sterically favored trans isomer.

That the isomer distributions are approximately the same regardless of the nature of (a) the substituent on the ketone, (b) the reaction solvent, or (c) the method of in situ preparation of the ketene, lends support to a near concerted mechanism. If a dipolar mechanism were operative, the substituents would be expected to stabilize the intermediate to different extents and thereby proportionally influence the isomer distributions. Aryl groups should stabilize such an intermediate better than alkyl substituents and therefore should be more reactive than alkyl ketones by such a mechanism. The opposite is observed; the alkyl-substituted ketones show little reactivity.
Similarly, solvent effects on the lifetimes of dipolar intermediates should be evident in the stereochemistry of the products. In more polar solvents the dipolar intermediate should be more highly solvated and have more time to rotate to the more favorable steric configuration. Finally, that the isomer ratios are approximately equal in dehydrohalogenation and dehalogenation systems suggests that both involve the same mechanism of cycloaddition and, considering the differences in the contents of the two systems, argues against the existence of a dipolar intermediate.

If the enhanced reactivity in dehalogenation systems is due to catalysis, then ionic or stepwise character of the mechanism should be increased over uncatalyzed reactions. Rather than decrease, however, the cis / trans increases in the cycloaddition of methylketene to chloral by in situ dehalogenation compared to in situ dehydrohalogenation. Therefore activation of chloral by zinc amalgam or zinc salts does not alter the ratio in a manner indicative of an ionic process.

If the cycloaddition of aldoketenes to chloral is assumed to be a near concerted process, conservation of orbital symmetry rules should predict the steric route of the cycloaddition. In the cycloaddition of ketenes to olefins, the Woodward-Hoffmann Rules allow a concerted process if the ketene, in its lowest unoccupied state, orthogonally approaches the olefin, in its highest occupied state, such that maximum
orbital overlap is obtained (32). In the bond formation, the ketene plays an antarafacial role and the olefin a suprafacial role. That is, from the transition state, the new bonds are formed on the same side of the olefin carbon-carbon double bond and on opposite sides of the ketene carbon-carbon double bond. The process necessitates rotation about and twisting of the ketene carbon-carbon bond as the new bonds are formed. The result of a sterically favored transition state and the symmetry allowed bond formation process is the sterically least favored isomer, e.g., in aldoketene-cyclopentadiene cycloadditions, the **endo** isomer (5, 10).

If an analogous process is assumed for aldoketene-chloral cycloadditions, the ketene in its lowest occupied state, approaches chloral, in its highest occupied state, in an orthogonal configuration. Four different transition states are possible, each different in energy by virtue of steric
Diagram A: The reaction involves the addition of a chloroform (CCl₃) molecule to an olefinic double bond, followed by a cycloaddition reaction to form a cyclic compound with a cis arrangement.

Diagram B: Similar to A, but the product has a trans arrangement.

Diagram C: Another reaction with chloroform addition followed by cycloaddition, resulting in a trans arrangement.

Diagram D: A cis arrangement is formed through a similar cycloaddition reaction.
interactions. In increasing energy, they are: $A$, with hydrogen-hydrogen interference; $B$, with R group-hydrogen interference; $C$, with trichloromethyl group-hydrogen interference; and $D$, with interference between the $R$ group and the trichloromethyl group.

Bond formation occurs in the direction dictated by bond polarities, i.e., to form a 2-oxetanone rather than a 3-oxetanone. In the formation of bonds, the ketene twists between its carbon atoms to obtain positive overlap for the C-C bond in the $\beta$-lactone and simultaneously rotates about an axis perpendicular to its molecular axis to form orbital overlap for the C-O bond.

This procedure results in production of the cis isomer from $A$, the trans isomer from $B$ and $C$ and the cis isomer from $D$. Contributions from transition state $D$, and to a lesser extent $C$, can be assumed to be small because of the overwhelming steric bulk of the trichloromethyl group.

Therefore, by a concerted process, cis-4-trichloro-2-oxetanones are predicted to arise from $A$, and trans-4-trichloromethyl-2-oxetanones from $B$ and, possibly from $C$. From steric considerations of $A$ and $B$, the cis isomer would be predicted to predominate.

When these theoretical predictions, based on the assumption the cycloaddition is concerted, are compared with experimentally observed isomer distributions, an agreement is seen. The cis
isomer predominates slightly. However, whether the cis predominance over trans is parallel to the contribution expected from A and the combined contributions of B and C is questionable.

In summary, aldoketene-chloral cycloadditions produce both cis- and trans-4-trichloromethyl-2-oxetanones with the sterically hindered cis isomer predominating. The isomer distribution is relatively constant for the systems investigated and appears insensitive to method of in situ generation of the ketene or solvent polarities. While stereospecificity or stereoselectivity is a prerequisite for, but no proof of a synchronous process, the stereochemical data and supporting data suggest a near concerted process. The observed isomer distributions are compatible with theoretical predictions based on the assumption that the cycloaddition is near concerted and proceeds with conservation of orbital symmetry.

Although side reactions are possible, dehalogenation of an haloacyl halide is a more effective method of accomplishing ketene-carbonyl cycloadditions in situ than dehydrohalogenation. Thus, dichloroketene adducts were obtained from simple ketones.

While a catalytic effect of zinc amalgam was demonstrated, the cycloadditions still primarily depend on the reactivities of the individual ketenes and carbonyl compounds. Thus, dichloroketene is more reactive than methylketene, and chloral is more reactive than simple aldehydes and ketones.
It is recognized that the stereochemical course of aldoketene-carbonyl cycloadditions poses more questions than it answers. The isomer distributions obtained were unexpected, but not as dramatic as the stereospecificity of aldoketene-imine or aldoketene-olefin cycloadditions. While the ratio of geometrical isomers suggest a near concerted process it neither conclusively proves a near concerted process, nor completely disproves the existence of a dipolar intermediate. The present work establishes the basis for a general investigation of ketene-carbonyl compounds.
3. __________________________, ibid., 109, 1575 (1967).
4. __________________________, ibid., 102, 64 (1969).
8. __________________________, ibid., 32, 612 (1967).


30. ibid., 44, 1619 (1911).


