Olefin Addition Reactions-1
Chlorination and Iodination

Evans Group Friday Seminar
Bichu Cheng
November 20th 2009
Outline

• Basic mechanism

• Applications in synthetic organic chemistry

• Total syntheses of halogen-containing natural products
Olefin Halogenations - Thermodynamics

<table>
<thead>
<tr>
<th>Ethylene halogenations</th>
<th>$\Delta H_r$ (kcal/mol)</th>
<th>calculated</th>
<th>lit. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_2 + C_2H_4 \rightarrow C_2H_4F_2$</td>
<td>-131</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>$Cl_2 + C_2H_4 \rightarrow C_2H_4Cl_2$</td>
<td>-44</td>
<td>-43.65 ± 0.15</td>
<td></td>
</tr>
<tr>
<td>$Br_2 + C_2H_4 \rightarrow C_2H_4Br_2$</td>
<td>-29</td>
<td>-28.90 ± 0.30</td>
<td></td>
</tr>
<tr>
<td>$I_2 + C_2H_4 \leftrightarrow C_2H_4I_2$</td>
<td>-2</td>
<td>-11.5 ± 0.2</td>
<td></td>
</tr>
</tbody>
</table>

Calculation based on bond dissociation energy (BDE).

$\Delta H_r = 2 \times \text{BDE(C-X)} + \text{BDE(C-C)} - \text{BDE(X-X)} - \text{BDE(C=C)}$

Lit. value obtained from NIST: http://webbook.nist.gov/chemistry/
Olefin Halogenation - Kinetics

Tools for following the kinetics of a reaction.
(Mayr J Phys Org Chem 2008, 21, 584)

Kinetics of Chlorine Addition to Styrenes in HOAc.
(Yates J. Org. Chem. 1980, 1401.)

rate law: \(-d[Cl_2]/dt = k[\text{Alkene}][Cl_2]\)

<table>
<thead>
<tr>
<th>olefin</th>
<th>(10^{-2}k) (L mol(^{-1}) s(^{-1}))</th>
<th>method</th>
</tr>
</thead>
<tbody>
<tr>
<td>styrene</td>
<td>72.1</td>
<td>stopped-flow</td>
</tr>
<tr>
<td>p-chlorostyrene</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>m-fluorostyrene</td>
<td>4.06</td>
<td></td>
</tr>
<tr>
<td>m-chlorostyrene</td>
<td>3.75</td>
<td></td>
</tr>
<tr>
<td>p-fluorostyrene</td>
<td>65.6</td>
<td></td>
</tr>
<tr>
<td>m-nitrostyrene</td>
<td>0.45</td>
<td>potentiometric</td>
</tr>
<tr>
<td>p-nitrostyrene</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>3,5-dinitrostyrene</td>
<td>0.081</td>
<td></td>
</tr>
<tr>
<td>(Z)-1-phenylpropene</td>
<td>145</td>
<td>stopped-flow</td>
</tr>
<tr>
<td>(E)-1-phenylpropene</td>
<td>&gt;1000</td>
<td></td>
</tr>
<tr>
<td>1-hexene</td>
<td>76.7</td>
<td></td>
</tr>
<tr>
<td>3-hexene</td>
<td>&gt;1000</td>
<td></td>
</tr>
</tbody>
</table>

Kinetics of iodine addition to alkenes
(Field J. Chem. Educ. 1987, 269.)

<table>
<thead>
<tr>
<th>Alkene</th>
<th>solvent</th>
<th>(t_{1/2}) (s)</th>
<th>(I_2) order</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclohexene</td>
<td>Cl(CH(_2)(_2))Cl</td>
<td>315</td>
<td>1st</td>
</tr>
<tr>
<td>cyclohexene</td>
<td>HOAc</td>
<td>525</td>
<td>2nd</td>
</tr>
<tr>
<td>1-pentene</td>
<td>Cl(CH(_2)(_2))Cl</td>
<td>2500</td>
<td>1st</td>
</tr>
<tr>
<td>1-pentene</td>
<td>HOAc</td>
<td>4400</td>
<td>2nd</td>
</tr>
<tr>
<td>cis-2-pentene</td>
<td>Cl(CH(_2)(_2))Cl</td>
<td>270</td>
<td>3rd</td>
</tr>
<tr>
<td>cis-2-pentene</td>
<td>HOAc</td>
<td>900</td>
<td>2nd</td>
</tr>
</tbody>
</table>

\([\text{alkene}] = 0.30 \text{ M}, [I_2] = 0.020 \text{ M}, \text{rt}\)

Kinetics of iodine addition to alkenes
(Robertson J. Chem. Soc. 1950, 2191.)

rate law: \(-d[I_2]/dt = k_4[\text{Alkene}][I_2]^3 + k_3[\text{Alkene}][I_2]^2\)

Alkenes: 1-hexene, 2-pentene, cyclopentene, 1-decene, undecenoic acid and oelic acid.

The first term being chief operative in non-polar solvents such as PhCl, CCl\(_4\) and CS\(_2\); and the second term in polar solvent iBu\(_2\)O, HOAc, and PhNO\(_2\).
Olefin Halogenations - General Mechanism

\[
\text{π complex} \quad \text{halonium ion} \quad \text{nonbridged cation}
\]
Olefin-Halogen $\pi$ Complex

♦ Labile and reactive. $\pi$ complex formation is followed rapidly by the formation of ionic intermediates and further chemical transformations. Mostly studied with Br$_2$.

♦ olefin chlorine $\pi$ complex was studied by low temperature spectroscopic methods and computations.

1. An C$_2$H$_4$/Cl$_2$ complex was prepared in a N$_2$ matrix at 20 K. Its UV and IR spectra have been recorded. Both IR data and CNDO/2 calculations favor a $C_{2v}$ symmetric complex. The CNDO/2 calculations predict that the Cl-Cl bond is orthogonal to the ethylene plane. The IR data give no evidence for or against this prediction. J. Mol. Struct. 1973, 205.

2. An ethane solution of C$_2$H$_4$/Cl$_2$ was studied by IR as a function of temperature and concentration. $\Delta G_f$ (0.9 kJ.mol$^{-1}$), $\Delta H_f$ (-8.6 kJ.mol$^{-1}$), $\Delta S_f$ (-70 J.mol$^{-1}$K$^{-1}$) were obtained. J. Mol. Struct. 1983, 269.

3. The rotational spectrum of a complex of $C_{2v}$ symmetry has been detected in a mixture of C$_2$H$_4$/Cl$_2$. Force constant $k = 7.05(5)$ N m$^{-1}$ (Force constant $k$ for a C-C bond is about 450 N m$^{-1}$) Chem. Comm. 1994, 1321. Angew. Chem. Ind. Ed. 1995, 51.
Bridged Halonium

- First proposed by Irving Roberts in 1937 to explain the stereospecific formation of trans halogenation products. (*J. Am. Chem. Soc.*, 1937, 947)

- NMR observation by George Olah.

From 1,2-dihaloalkane (*J. Am. Chem. Soc.*, 1967, 4744)

\[
\begin{align*}
\text{1,2-dihaloalkane} & \xrightarrow{\text{SbF}_5-\text{SO}_2} \quad \text{haloalkane} \\
\text{or} & \quad \text{haloalkane} \\
\text{X} & \quad \text{X} \\
\text{X} & \quad \text{F} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>X</th>
<th>δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>2.72(s)</td>
</tr>
<tr>
<td>Br</td>
<td>2.86(s)</td>
</tr>
<tr>
<td>I</td>
<td>3.05(s)</td>
</tr>
</tbody>
</table>

- no change in \(^1\text{H} \text{NMR}\) down to -95 °C; in \(\text{SO}_2\text{ClF}\), no change down to -120 ~ -130°C


\[
\begin{align*}
\text{H}_2\text{C} = \text{CH}_2 & \xrightarrow{\text{ICN-} \text{SbF}_5} \quad \text{SbF}_5\text{CN}^- \\
\text{polymeric material with BrCN-} \text{SbF}_5 & \quad \text{and no reaction with ClCN-} \text{SbF}_5 \\
\text{XCN-} \text{SbF}_5 & \xrightarrow{\text{X = Br, I}} \quad \text{SbF}_5\text{CN}^- \\
\end{align*}
\]
Bridged Halonium: Isolation

![adamantylideneadamantane](image)

\( \text{Ad=Ad} \)


\[
\text{Ad=Ad} \xrightarrow{\text{Cl}_2/\text{CCl}_4 \ -20 \ ^\circ \text{C}} \text{white precipitate} \xrightarrow{10 \ ^\circ \text{C}} \text{Ad=Ad} \text{ and disubstituted isomers}
\]


\[
\begin{align*}
\text{Ad=Ad} + \text{OsO}_4 & \xrightarrow{\text{rt}} \text{observed by UV-visible spectra} \\
\rightarrow & \text{Ad=Ad OsO}_4
\end{align*}
\]

Unexpected halonium formation

- cis-chlorination reagents

\[
\begin{align*}
2 \text{MoOCl}_4 + \text{Ad=Ad} & \xrightarrow{-78 \ ^\circ \text{C}} \text{gold, paramagnetic solid} \\
\text{elemental analysis, IR,} & \\
\text{cis-chlorination} & \\
\text{reagents} & \\
2 \text{SbCl}_5 + \text{Ad=Ad} & \xrightarrow{-78 \ ^\circ \text{C}} \text{white, diamagnetic solid} \\
\text{elemental analysis, IR} & \\
\text{and } ^{13}\text{C NMR} &
\end{align*}
\]
Bridge Iodonium: x-Ray Structure and Reactivity


- Selected Interatomic Distances and Angles from X-ray Diffraction and from *ab Initio* SCF Calculation.

<table>
<thead>
<tr>
<th>Interatomic Distances (Å)</th>
<th>observed</th>
<th>calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{10}C_{20}</td>
<td>1.454(6)</td>
<td>1.485</td>
</tr>
<tr>
<td>I-C_{10}</td>
<td>2.362(6)</td>
<td>2.389</td>
</tr>
<tr>
<td>I-C_{20}</td>
<td>2.338(6)</td>
<td>2.389</td>
</tr>
<tr>
<td>I-O_{4}</td>
<td>2.630(4)</td>
<td>2.630</td>
</tr>
<tr>
<td>O_{4}O_{1}</td>
<td>2.796(8)</td>
<td>2.796</td>
</tr>
<tr>
<td>O_{4}O_{3}</td>
<td>2.752(8)</td>
<td>2.752</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interatomic Angles (deg)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C-C_{10}C_{20}</td>
<td>110.6(5)</td>
<td>110.9</td>
</tr>
<tr>
<td>C-C_{20}I</td>
<td>111.8(5)</td>
<td>110.9</td>
</tr>
<tr>
<td>C_{10}I-C_{20}</td>
<td>36.0(1)</td>
<td>36.2</td>
</tr>
<tr>
<td>I-C_{10}C_{20}</td>
<td>71.1(4)</td>
<td>71.9</td>
</tr>
<tr>
<td>I-C_{20}C_{10}</td>
<td>72.9(4)</td>
<td>71.9</td>
</tr>
</tbody>
</table>

- Reactivity: I⁺ site exchange

\[
\text{Ad}+\text{Ad} + \text{TfO}⁻ \xrightleftharpoons[78 \, ^\circ\text{C}]{\text{second-order rate constant}} 7.6 \pm 0.8 \times 10^6 \, \text{M}^{-1} \, \text{s}^{-1} \text{Ad}⁺ \text{Ad} \xrightarrow{} \text{Ad}⁺\text{Ad} + \text{TfO}⁻
\]

- Two ORTEP views of the iodonium momohydrate.


\[
R = \text{H}, \, n = 2, 3, 4 \\
R = \text{CH}_3, \, n = 3
\]
Bridged Chloronium: x-Ray Structure and Reactivity

♦ Preparation of chloronium by Cl⁺ transfer
(Kochi Chem. Comm. 1998, 927.)

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, 0°C & \quad (\text{Kochi J. Org. Chem. 2002, 67, 5106})
\end{align*}
\]

♦ ORTEP diagram of two chloroniums

an ineffective Cl⁺ transfer reagent; a one-electron oxidant
Outline

• Basic mechanisms

• Applications in synthetic organic chemistry

• Total syntheses of halogen-containing natural products
Dichlorination

- $\text{Et}_4\text{NCl}_3$: A benchstable equivalent to $\text{Cl}_2$

$$\text{Et}_4\text{NCl} + \text{Cl}_2 \rightarrow \text{Et}_4\text{NCl}_3$$

The content of active chloride was 3.2 mmol g$^{-1}$, and no decrease in activity was observed upon storage for several months at room temperature.

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{RCH=CHR'}$</td>
<td>$\text{RCHClCHClR'}$</td>
</tr>
<tr>
<td>$\text{R} \equiv \equiv \text{R'}$</td>
<td>$\text{RCl} \equiv \equiv \text{R'}$</td>
</tr>
<tr>
<td>$\text{PhOR}$</td>
<td>$\text{Cl} \equiv \equiv \text{R'}$</td>
</tr>
<tr>
<td>$\text{RCOCHR}_{2}\text{CO}_2\text{R'}$</td>
<td>$\text{RCOClCR}_{2}\text{CO}_2\text{R'}$</td>
</tr>
<tr>
<td>$\text{RCOCH}_{2}\text{R'}$</td>
<td>$\text{RCOCHClR'}$</td>
</tr>
<tr>
<td>$\text{RCH}_{2}\text{CHO}$</td>
<td>$\text{RCCl}_2\text{CHO}$</td>
</tr>
<tr>
<td>$\text{HO}$</td>
<td>$\text{O}$</td>
</tr>
</tbody>
</table>

- First reagent-controlled highly stereoselective olefin dichlorination

$$\text{BH}_3\cdot\text{THF} (4 \text{ equiv.}), \quad (\text{S})-\text{9} (4 \text{ equiv.}) \quad \text{Cl}_2, \text{THF, } -78^\circ\text{C} \quad (93\% \text{ yield, } 87\% \text{ ee}; \quad 95\% \text{ ee after crystallization})$$

$$\text{OH} \quad \text{Cl} \quad \text{Cl} \quad \text{OH} \quad \text{Cl} \quad \text{OH}$$

$$\text{MOMO}^- \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{O}$$

$$\text{(-)-Napyradiomycin A1}$$


Iodination

- **Common I⁺ source:** \( I_2, \text{ICl, IBr, IOAc, NIS, Py}_2\text{IBF}_4 \).
- **Kinetic control:** \( I_2/\text{NaHCO}_3, \text{NIS in CHCl}_3, I_2 \text{ in CHCl}_3 \) and \( I_2 \text{ in pyridine/THF} \);
  **Thermodynamic control:** \( I_2 \text{ in MeCN} \).
- Diiodination of olefin is reversible and product usually unstable.
- More common and useful: electrophilic iodine induced alkene functionalization with other external and internal nucleophiles.
  - **External Nucleophile**
    Regiochemistry is controlled by a combination of electronic (Markovnikov rule), stereoelectronic (trans diaxial addition to cyclohexenes) and steric factors.
    some stereoselective examples

![Chemical structures](image)


- **Internal Nucleophile**
  Additional conformational and entropic factors.
  General preference for cyclization: 5-*endo* > 4-*exo*, 5-*exo* > 6-*endo*, 6-*exo* > 7-*endo*.

1,2-Cis Induction in Iodolactonization and Intramolecular Iodoetherification of Allylic Alcohol Derivatives

- **1,2-cis Selective Iodolactonization**

\[
\text{HO-CH=R-CH=O} \xrightarrow{\text{I}_2, \text{NaHCO}_3} \text{HO-CH=IR-CH=O}
\]

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>yield</th>
<th>cis:trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>66%</td>
<td>93:7</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>49%</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>74%</td>
<td>95:5</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>82%</td>
<td>96:4</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>8%</td>
<td>&lt;10:90</td>
</tr>
</tbody>
</table>

- **1,2-cis Selective Iodoetherification**

\[
\text{HO-CH=R-CH=O} \xrightarrow{\text{I}_2, \text{NaHCO}_3} \text{HO-CH=IR-CH=O} + \text{HO-CH=IR-CH=O}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>yield</th>
<th>cis:trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>87%</td>
<td>95:5</td>
</tr>
<tr>
<td>Me</td>
<td>94%</td>
<td>91:9</td>
</tr>
<tr>
<td>i-Pr</td>
<td>73%</td>
<td>100:0</td>
</tr>
</tbody>
</table>

\[
\text{Ph-CH=CH=CH-CH=O} \xrightarrow{\text{I}_2, \text{NaHCO}_3} \text{Ph-CH=CH=CH-CH=O} + \text{Ph-CH=CH=CH-CH=O}
\]

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>yield</th>
<th>cis:trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>98%</td>
<td>100:0</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>93%</td>
<td>98:2</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>79%</td>
<td>93:7</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>87%</td>
<td>19:81</td>
</tr>
</tbody>
</table>

\[
\text{Ph-CH=CH=CH-CH=O} \xrightarrow{\text{I}_2, \text{NaHCO}_3} \text{Ph-CH=CH=CH-CH=O} + \text{Ph-CH=CH=CH-CH=O}
\]

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>yield</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>81%</td>
<td>94:6:0</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>94%</td>
<td>39:61:0</td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>82%</td>
<td>13:1:86</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>81%</td>
<td>27:0:73</td>
</tr>
</tbody>
</table>


A complete turnover in olefin diastereofacial selectivity observed when adding internal and external nucleophiles

**General Observation:**
For electrophiles that react viaonium intermediates (I₂, Br₂, Hg(OAc)₂, PhSeCl), the major diastereomer from electrophile-induced cyclization is opposite to that observed in the analogous intermolecular electrophilic addition.

For a review of electrophilic induced olefin cyclization reactions see:

**Chamberlin & Hehre's Rationalization**
- "Facial preferences in electrophilic addition reactions are not invariant with respect to the location of the transition state along the reaction coordinate."
- Change in diastereoselectivity is a consequence of a change in the rate-limiting step
  - Addition reactions: Formation of anonium ion intermediate
    (subsequently trapped by a Nu from the medium)
  - Cyclization reactions: Intramolecular attack on a σ-complex (not an onium ion)
- Analysis of the stereoselectivity of electrophilic addition to chiral olefins:
  1. Relative abundances of conformational minima
  2. Relative reactivities of the available forms
  3. Stereoselectivities of the individual conformers


**Hehre's Analysis**
- Addition product
- Favored ground-state conformer
- Distavored σ-complex
- RDS
- More reactive ground-state conformer
- Favored σ-complex
- Distavored iodonium ion
- Cyclization product

Houk: Argument for the "inside alkoxy effect" in σ-complex formation
- σ-complex cyclizes if R contains a Nu and its formation is rate determining
- Onium ion formation is rate determining in the addition reactions
- "The presence or absence of an internal nucleophile acts to determine the stereochemical outcome of the reaction by modifying the nature (timing) of transition state."
1,3-Trans Induction: Halolactonization of α- and α,β-substituted γ,δ-unsaturated amides

♦ 1,3-Trans-Selective Lactonization of 2-substituted Amides and Thioamides

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>Y</th>
<th>yield</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>O</td>
<td>85</td>
<td>90:10</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>H</td>
<td>O</td>
<td>84</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>Me</td>
<td>O</td>
<td>82</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>H</td>
<td>S</td>
<td>42</td>
<td>91:9</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>H</td>
<td>S</td>
<td>67</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

♦ Stereoslectivity due to A(1,3) strain between R₁ and N-methyl groups

![Chemical structure](image)


♦ Stereoselective Iodolactonization of 2,3-Disubstituted N,N-Dimethyl-4-penteneamide

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>yield</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>63</td>
<td>97:3</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>63</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>88</td>
<td>20:80</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>84</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>OAc</td>
<td>H</td>
<td>H</td>
<td>68</td>
<td>45:55</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>OAc</td>
<td>H</td>
<td>95</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>OAc</td>
<td>Me</td>
<td>75</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>

allylic OH
1,2-cis directing ability
Double Diastereoselection in the Iodolactonization of 1,6-Heptadien-4-Carboxylic Acids

- Diastereoselective Iodolactonization of 1,6-Heptadien-4-Carboxylic Acids

\[
\text{COOH} \quad \xrightarrow{\text{I}_2, \text{NaHCO}_3} \quad \text{COOH} \\
1 \quad 3 \quad 5 \quad 6 \quad 7 \quad 8
\]

Olefin selectivity: acyclic conformational control
Minimizing gauche interaction in the Newman projection

- Olefin selectivity: acyclic conformational control

\[
\begin{align*}
\text{COOH and C1 olefin} & \quad \text{COOH and C6 olefin} \\
\text{in close proximity} & \quad \text{antiperiplanar}
\end{align*}
\]

Kurth, M. J  
Stereoelectronic Effects in Iodoetherification of Allylic Alcohol Derivatives

- **Trans** Selectivity in Iodoetherification of 1
  
  \[
  \text{HO-CH=CH-CO}_2\text{Et} \xrightarrow{\text{I}_2, \text{NaHCO}_3} \text{HO-CH=CH-CO}_2\text{Et} \xrightarrow{\text{THF}} \text{I}\text{HO-CH=CH-CO}_2\text{Et} \quad \text{91\%}
  \]
  

- Proposed two trans-predictive transition states
  
  - sterically favored
  
  - stereoelectronically favored

- Diols 3 and 5 as probes to differentiate between two trans-predictive transition states
  
  - 3 reacts faster if steric controlled
  
  - 5 reacts faster if torsional strain minimization and stereoelectronic arguments are involved
Stereoelectronic Effects in Iodoetherification of Allylic Alcohol Derivatives

- Two-directional synthesis: compound with pseudo C₂ axis of symmetry as a probe.

![Chemical structures and reactions](image)

- Path A is sterically favored.
- Path B is stereoelectronically favored.
**Iodoetherifications Outcome and Conclusion**

**Iodoetherifications of Diols 3 and 5 under Kinetic Conditions**

![Chemical Structures]

**Operative transition states**

**Group-selective iodoetherification**

**Conclusion**

Both stereoelectronic effects and allylic 1,3-strain are important controlling factors in the cyclofunctionalization reaction when an electron withdrawing group is at the allylic position.
Reagent-Controlled Stereoselective Iodinations

Chiral reagents

\[ \text{Chiral reagents} \]

\[
\begin{array}{c}
\text{MeO} \\
\text{AcO} \\
\text{Et} \\
\text{N} \\
\text{I} + \text{BF}_4^- \\
\end{array}
\]

5-exo iodolactonisation up to 14% ee


\[
\begin{array}{c}
\text{NH}_2 \\
\text{I} \\
\end{array}
\]

5-exo iodolactonisation up to 50% ee


Chiral catalysts

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{O} \\
\text{O} \\
\text{Ti} \\
\end{array}
\]

Ti(TADDOLate)$_2$

Taguchi T., Synlett, 1999, 1191.


♦ Iodocarbocyclization

\[
\begin{array}{c}
\text{CO}_2\text{R} \\
\text{CO}_2\text{R} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_2 \\
\text{CMe}_2 \\
\text{O} \\
\text{R} = \text{Bn, Me; DMP} = 2,6\text{-dimethoxypyridine.}
\end{array}
\]

60-87% yield, 96-99% ee

♦ Enantiotopic group selective reaction

\[
\begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{CO}_2\text{CH}_3
\end{array}
\]

as above

67% yield 95% ee

\[
\begin{array}{c}
\text{CO}_2\text{CH}_3 \\
\text{CO}_2\text{CH}_3
\end{array}
\]

as above

80% yield 99% ee

1. NCS, toluene, rt, 30 min.
2. I$_2$, -78 ºC
3. -78 ºC, 20h

67-90% ee
Enantioselective halocyclization of polyprenoids induced by nucleophilic phosphoramidites

- Nucleophilic promoters versus Lewis acid promoters for the activation of N-halosuccinimides.

- Activities of achiral nucleophiles for halopolyacyclization of 1.

- Enantioselective halocyclization induced by chiral nucleophilic promoters

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Yield of 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(nBu)_3</td>
<td>99</td>
</tr>
<tr>
<td>P[C_6H_4(p-OMe)]_3</td>
<td>87</td>
</tr>
<tr>
<td>PPh_3</td>
<td>67</td>
</tr>
<tr>
<td>P(OPh)_3</td>
<td>51</td>
</tr>
<tr>
<td>DABCO</td>
<td>0</td>
</tr>
<tr>
<td>DMAP</td>
<td>0</td>
</tr>
<tr>
<td>No catalyst</td>
<td>3</td>
</tr>
</tbody>
</table>

Enantioselective halocyclization of polyprenoids induced by nucleophilic phosphoramidites
Outline

- Basic mechanisms
- Applications in synthetic organic chemistry
- Total syntheses of halogen-containing natural products
Halogenated Natural Products

As of 2006, more than 4500 halogenated natural products have been discovered, though it is likely to be a substantially incomplete inventory. These include 30 organofluorines, 2300 organochlorines, 2100 organobromines, and 120 organoiodines.

Chlorosulfolipids

Freshwater algae

Mussels

Biochemistry 1970, 9, 3110-3126

J. Nat. Prod. 1994, 57, 524-527

J. Org. Chem. 2009, 74, 6016-6024


X = H Tetrahedron 2004, 60, 7093–7098
**Stereoselective Dichlorination of Allylic Alcohol Derivatives**

- Dichlorination of (Z)-allylic alcohol derivatives

![Chemical structures]

- Stereoselective dichlorination (TCA = trichloroacetyl)

![Chemical structures]

- Stereochemical proof: transform to epoxide or Eq 1

![Chemical structures]

- Synthesis of a stereotetrad relevant to chlorosulfolipid

![Chemical structures]

Synthesis and Characterization of All Four Diastereomers of 3,4-Dichloro-2-pentanol

Kishi's Universal NMR Databases


Synthesis and Characterization of All Four Diastereomers

![Chemical Structure]

20% + 11% + 44% + 30% → TsCl

x-Ray structure

Comparison with natural chlorosulfolipid

![Chemical Structure]

Conclusion

“The high degree of conformational order that characterizes the chlorosulfolipids might only be possible when more than three contiguous stereogenic centers are present and working in concert.”

Vanderwal C.D.
Conformational and Configurational Analysis of Trichlorinated Hexane-1,2- and -1,3-diols

- Trichlorinated hexane-1,2- and -1,3-diols: stereotetrad of chlorosulfolipid

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Et} \\
& \quad \text{trans} \\
& \quad \text{cis} \\
\end{align*}
\]

- Coupling constants for model system

\[
\begin{align*}
^3J(H2,H3) & = +2.9 \text{ Hz} \quad \text{small} \\
^3J(H2,C4) & = +0.8 \text{ Hz} \quad \text{small} \\
^3J(H3,C1) & = +4.7 \text{ Hz} \quad \text{large} \\
^2J(H2,C3) & = +3.6 \text{ Hz} \quad \text{small} \\
^2J(H3,C2) & = -4.5 \text{ Hz} \quad \text{large} \\
\end{align*}
\]

- Fragments Prepared (Black) and Spectroscopically Examined

J-Based-Configuration Analysis Method for Polychlorinated Systems

- NMR Spectroscopic Analysis: HSQC-HECADE, HMBC, NOESY

For most 1,2- and 1,3-diols, the data were interpreted as the existence of one predominating conformer in solution.

- Generalized homo- and heteronuclear coupling constants for vicinal dichlorides and chlorohydrins as a function of the dihedral angle.

- $^3J(H,H)$-coupling constants
  - $^3J(H,H)$-coupling constants
    - $^3J(H,H)$ large: +7.5 - 10.5 Hz
    - $^3J(H,H)$ small: +1.0 - +3.5 Hz

- $^3J(H,C)$-coupling constants
  - $^3J(H,C)$ large: +4.5 - +5.0 Hz
  - $^3J(H,C)$ small: 0.0 - +3.0 Hz

- $^2J(H,C)$-coupling constants
  - $^2J(H,C)$ small: -0.5 - +4.0 Hz
  - $^2J(H,C)$ large: -3.5 - -6.5 Hz
Comparison of the X-ray Structures of Diols with the Predominant Conformation in Solution

<table>
<thead>
<tr>
<th>Crystal structure (ORTEP diagram)</th>
<th>Perspective formula</th>
<th>Crystal structure (ORTEP diagram)</th>
<th>Perspective formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>X-Ray = NMR[^6]</td>
<td><img src="image2.png" alt="Image" /></td>
<td>X-Ray = NMR[^a]</td>
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<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>X-Ray = NMR[^6]</td>
<td><img src="image4.png" alt="Image" /></td>
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<td>X-Ray = NMR[^b]</td>
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<tr>
<td><img src="image13.png" alt="Image" /></td>
<td>X-Ray = NMR[^6]</td>
<td><img src="image14.png" alt="Image" /></td>
<td>X-Ray = NMR[^b]</td>
</tr>
<tr>
<td><img src="image15.png" alt="Image" /></td>
<td>X-Ray = NMR[^6]</td>
<td><img src="image16.png" alt="Image" /></td>
<td>X-Ray = NMR[^b]</td>
</tr>
</tbody>
</table>

[^a]: Additional note
[^b]: Additional note
[^6]: Additional note
Conformational Analysis of Trichlorohexanediols.

- The dominant determinant of the preferred conformation is the minimization of syn-pentane interactions.

Preferred conformation of 2,4-dichloropentane

Both conformers avoid syn-pentane interactions
A value: Cl(0.6), Me(1.7)
Bond length: C-Cl(1.8Å), C-C(1.5Å)

- Gauche-effect and dipole minimization

32 Solid State (X-Ray)

32 Solution (NMR)

41 Solid State (X-Ray)

41 Solution (NMR)
Total Synthesis of Chlorosulfolipids-1

Initial synthetic studies of chlorosulpholipid

Revised and completion of total synthesis of chlorosulpholipid

Total Synthesis of Chlorosulfolipids-2