Benign Molecular Design

Alvise Perosa
Dipartimento di Scienze Ambientali
Università Ca’ Foscari di Venezia
alvise@unive.it

Today’s Outline:

1. Chemistry vs. Green Chemistry
2. Definitions
3. How do we measure greenness?
4. Examples of green and…
5. … of very un-green chemistry
6. Tools: green solvents and catalysis

1. REACH: REGISTRATION, EVALUATION, AUTHORISATION AND RESTRICTION OF CHEMICAL SUBSTANCES
Chemistry makes life better!
Green Chemistry:

Sustainable development

**Sustainability**: “Given reasonable assumption concerning progress in the technology and the activities of a civilization, a sustainable civilization is one in which the net sum of the daily activities of the people who comprise it, individually and collectively, can be carried on into the indefinite future, without undermining the ability of future generations to live with at least a comparably advantageous welfare”.

**Green Chemistry: definition 2**

Green chemistry efficiently utilises (preferably renewable) raw materials (and energy), it eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.


**Green Chemistry: 12 principles**

- Prevent waste
- Design safer chemicals and products
- Design less hazardous chemical syntheses
- Use renewable feedstocks
- Use catalysts
- Avoid chemical derivatives
- Maximize atom economy
- Use safer solvents and reaction conditions
- Increase energy efficiency
- Design chemicals and products to degrade after use
- Analyze in real time to prevent pollution
- Minimize the potential for accidents

*common sense?*

PRODUCTIVELY

Condensed Principles of Green Chemistry
- Prevent wastes
- Renewable materials
- Omit derivatization steps
- Degradable chemical products
- Use safe synthetic methods
- Catalytic reagents
- Temperature, Pressure ambient
- In-Process Monitoring
- Very few auxiliary substances
- E-Factor, maximise feed in product
- Low toxicity of chemical products
- Yes, it is safe

Green Chemistry: metrics 1

<table>
<thead>
<tr>
<th>Industry segment</th>
<th>Product tonnage</th>
<th>E Factor (kg waste/kg product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil refining</td>
<td>$10^9$–$10^{18}$</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Bulk chemicals</td>
<td>$10^4$–$10^6$</td>
<td>&lt;1–5</td>
</tr>
<tr>
<td>Fine chemicals</td>
<td>$10^3$–$10^4$</td>
<td>5–50</td>
</tr>
<tr>
<td>Pharmaceuticals</td>
<td>$10$–$10^4$</td>
<td>25–100</td>
</tr>
</tbody>
</table>

Roger A. Sheldon, *Chem. Ind.*, 1992, 903
Roger A. Sheldon, *Green Chem.*, 2007, 9, 1273
Green Chemistry: metrics 2

Atom economy

\[
\% \text{ AE} = \frac{\text{molecular weight (g mol}^{-1}\text{) product}}{\sum \text{molecular weights of all reagents}}
\]


Atom economy: an example

1. Chlorohydrin process

\[
\begin{align*}
\text{ClCH}_2\text{CH}_2\text{OH} + \text{HCl} & \rightarrow \text{ClCH}_2\text{CH}_2\text{OH} + \text{HCl} \\
\text{Ca(OH)}_2 & \rightarrow \text{CaO}_2 + 2 \text{H}_{2}\text{O}
\end{align*}
\]

Overall:

\[
\begin{align*}
\text{H}_{2}\text{O} + \text{Cl}_{2} + \text{Ca(OH)}_2 & \rightarrow \text{CaCl}_2 + \text{Cl}_{2} + \text{H}_{2}\text{O} \quad 35\% \text{ atom utilization}
\end{align*}
\]

2. Dried oxidation

\[
\begin{align*}
\text{H}_{2}\text{O} + 0.5 \text{O}_2 & \rightarrow \text{H}_{2}\text{O} \quad 100\% \text{ atom utilization}
\end{align*}
\]

\[E_{\text{th}} = \frac{75}{25} = 3\]

\[E_{\text{th}} = \frac{0}{100} = 0\]

Theoretical E factor (\(E_{\text{th}}\)) is the MW of wasted atoms divided by the MW of product (always much lower than the true E).
Traditional Boot's synthesis of ibuprofen:

\[
\begin{align*}
\text{Traditional Boot's synthesis of ibuprofen} & \quad (\text{CH}_3\text{CO})_2\text{O} \quad \xrightarrow{\text{Ac}_2\text{O}} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{H}^+} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{NaOC}_2\text{H}_5} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{AlCl}_3} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{HNO}_2} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{H}^+} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{Ibuprofen} \\
\end{align*}
\]

6 steps

BHC green synthesis of ibuprofen:

\[
\begin{align*}
\text{BHC green synthesis of ibuprofen:} & \quad (\text{CH}_3\text{CO})_2\text{O} \quad \xrightarrow{\text{HF}} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{Ibuprofen} \\
& \quad \xrightarrow{\text{CO, Pd}} \quad \text{Ibuprofen} \\
\end{align*}
\]

3 steps
### Reagent Used in ibuprofen

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Formula</th>
<th>M&lt;sub&gt;r&lt;/sub&gt;</th>
<th>Unused in ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;14&lt;/sub&gt;</td>
<td>134</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;</td>
<td>133</td>
</tr>
<tr>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>102</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>27</td>
</tr>
<tr>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;ClO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>122.5</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>13</td>
</tr>
<tr>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;ONa</td>
<td>68</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;1&lt;/sub&gt;</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NH&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>145.5</td>
</tr>
</tbody>
</table>

#### Total Ibuprofen Waste products
- C<sub>20</sub>H<sub>42</sub>NO<sub>10</sub>ClN: 514.5
- C<sub>13</sub>H<sub>18</sub>O<sub>2</sub>: 206
- C<sub>7</sub>H<sub>24</sub>NO<sub>8</sub>ClN: 308.5

### Atom economy in the Boots' synthesis of ibuprofen
- 40% Atom economy
- 77% Atom economy in the green synthesis of ibuprofen

http://www.rsc.org/education/teachers/learnnet/green/ibuprofen/home.htm

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### Dimethylcarbonate: an alternative green methylating reagent

- **Toxic!**

Dimethylcarbonate (DMC) is a non-toxic alternative to methyl halides used in the synthesis of ibuprofen.

\[ \text{DMC} \rightarrow \text{Ibuprofen} \]
Redesign of the Sertraline Process

- Sertraline: active ingredient in Zoloft (Pfizer).
- In 2007, it was the most prescribed antidepressant on the U.S. retail market, with 29,652,000 prescriptions
- Combined process
  - Doubled yield
  - Ethanol replaced CH₂Cl₂, THF, toluene, hexane
  - Eliminated use of 140 metric tons/year TiCl₄
  - Eliminated 150 metric tons/year 35% HCl
Alternative Synthesis of Cytovene

- antiviral agent used in the treatment of cytomegalovirus (CMV) retinitis infections
- AIDS and solid-tissue transplant patients
- Improved synthesis
  - reduced chemical processing steps from 6 to 2
  - reduced number of reagents and intermediates from 22 to 11
  - eliminated 1.12 million kg/year liquid waste
  - eliminated 25,300 kg/year solid waste
  - increased overall yield by 25%

Alternative Synthesis

- Improved synthesis of a central nervous system compound (Eli Lilly & Co)
  - interdisciplinary approach, combining chemistry, microbiology, and engineering
- For every 100 kg product,
  - 300 kg chromium waste eliminated
  - 34,000 liters solvent eliminated
Alternative Synthesis

UN-GREEN CHEMISTRY
SEVESO: DIOXIN CONTAMINATION

Cloroform (a disinfectant)

2,3,7,8-tetrachlorodibenzo-p-dioxin

Dichloro-Diphenyl-Trichloroethane

DDT
Thalidomide

Thalidomide was used by pregnant women in Europe to lessen the effects of morning sickness. About 10000 children were born with acute birth defects, in many cases in the form of missing or deformed limbs.

One enantiomer is active as a drug, the opposite one is teratogenic.

BHOPAL disaster

December 3rd 1984, the Union Carbide plant in Bhopal (India) discharged 42 tons of methyl isocyanate into the atmosphere exposing over 500,000 people.
13 November 2005
China National Petroleum Co. in Jilin.

An explosion dumped in the Songhua river 100 tons of benzene, along with 2 ton. of nitrobenzene, aniline, and xylene.

13 November: accident
24 November: in Harbin drinking water supplies are closed

Paracelsus

Paracelsus who was born Philippus Aureolus (1493-1541) took the pseudonym of Theophrastus Bombastus Von Hohenheim. He became a renown physician, alchemist and occultist.

“Everything is toxic. It is simply depends on the dose.”
Green chemistry principle no. 8: Use safer solvents and reaction conditions.

An old example: benzene vs. toluene:

\[
\text{C}_6\text{H}_6 + \text{O}_2 + \text{NADPH} + \text{H}^+ \rightarrow \text{C}_6\text{H}_5\text{CH}_2\text{OH}
\]

\[
\text{C}_6\text{H}_5\text{CH}_3 + \text{O}_2 + \text{NADPH} + \text{H}^+ \rightarrow \text{C}_6\text{H}_5\text{CH}_2\text{OH}
\]

Phase I of biotransformation of toluene and benzene within monoxygenase system in Cytochrome P450
Green solvents in place of toxic and VOC-generating ones

An example: supercritical CO₂
Extraction of organic compounds using supercritical CO₂

Dry-cleaning using scCO₂
Green solvents in place of toxic and VOC-generating ones

Another example: Ionic liquids

- Made entirely of ions
- Molten at or around room temperature (mp < 100 °C)
- No vapour pressure

Table salt NaCl
mp = 801 °C

Ionic liquids can be designed to be soluble “as needed”.

A triphasic organic-ionic liquid – aqueous system
The best solvent is no solvent

An example of solventless synthesis with an ionic liquid catalyst:

\[
\text{O} \quad + \quad \text{NO}_2 \quad \xrightarrow{\text{liquido ionico catalizzatore}} \quad \text{O} \quad \text{CH}_3
\]
What about water?

“On water” reactions by B. Sharpless (Nobel Prize 2001)

Catalysis

Green chemistry principle no. 5: Use catalysis.

A CATALYST IS SOMETHING THAT MAKES A CHEMICAL REACTION GO FASTER, WITHOUT BEING CONSUMED IN THE PROCESS
Catalysis

Olefin metathesis

(Catalysis Nobel Prize 2005)

Catalytic metathesis

Shell Higher Olefin Process

1 million tons/year
Enantioselective catalysis

Particularly in pharmaceutical chemistry, drugs are often chiral, and only one of the enantiomers is active.

In the best case the other enantiomer is useless (50% waste). In the worst case it’s toxic (remember thalidomide).

Why get one for the price of two?

Of the active enantiomer only 50% is used in the body on average.

So we might be producing four times more active ingredient than needed!

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Step 1: Enantioselective catalysis

Example: Monsanto’s L-DOPA process

\[
\begin{align*}
\text{AcO} & \quad \text{OMe} & \quad \text{COOH} & \quad \text{NHCOCH}_3 \\
\text{AcO} & \quad \text{OMe} & \quad \text{COOH} & \quad \text{NH}_2
\end{align*}
\]

95 % ee
20000 tons
Step 2: Targeted delivery

By coupling enantioselective catalysis with targeted drug delivery 100% of the drug is used.

So: why do we need Green Chemistry?

Answer: to allow future generations to live at least as well as us, and to live better and save money in the process.

We would need approximately 3.5 earths if all the 6.6 billion people lived with our standards.

http://sustainability.publicradio.org/consumerconsequences/
Thank you!

alvise@unive.it