The Role of Atom Economy in the Ideal Synthesis

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Introduction:

Knowledge of synthetic organic chemistry has grown tremendously over the past century. Organic reactions continually evolve to become increasingly high yielding, efficient and selective (chemo-, regio-, enantio-, diastereo-). Coupled with these advancements there exists an intrinsic goal of making chemistry more sustainable or environmentally friendly, a desire to produce less waste, use fewer solvents, run reactions with less thermal energy, etc. Recently, Tucker defined sustainable chemistry as “neither a new type of chemistry nor an environmental movement, a condemnation of industry, new technology, or ‘what we do already’...(but) a new environmental priority when accomplishing the science already being performed…regardless of the scientific discipline or the techniques applied.”¹ Such “green” chemistry is governed by 12 principles² that any chemist should consider in planning syntheses. Some of these concepts include the minimal use of hazardous reagents/reactants, the prevention of waste and byproducts, a high degree of incorporating reactants into the desired target, and a heavy emphasis on the use of catalytic processes.³

Of these principles, the maximization of starting materials into the desired product has gained popularity over the past twenty years in an increasing effort to make all chemical processes greener.³ This movement has been felt in all facets of synthetic chemistry ranging from industrial practices to general synthetic research: (1) Pharmacia and Upjohn have developed newer routes to the steroid intermediate bisnoraldehyde that eliminates heavy metal waste,⁴ and (2) an increasing number of syntheses have been recently reported that employ little to no protecting groups thereby maximizing output while minimizing waste.⁵ Focusing on such “green” or sustainable chemistry offers numerous economical and environmental advantages. The incorporation of more reactant into a desired product presumably reduces waste thereby diminishing exogenous costs associated with cleanup, purchasing starting materials and solvents, etc.
Atom Economy Defined

Trost is credited with coining the term “atom economy,” which is a measurement of how much of the reactants remain in the final product in a chemical reaction.\(^6\) Mathematically, the atom economy (AE) is the molecular weight of the product divided by the molecular weights of all the reactants (Equation 1). In his 1991 *Science* publication, Trost challenged chemists to pursue “greener chemistry” by making syntheses more atomically economical. In an ideal situation, reactions with the best atom economies would involve the unification of two stoichiometric reactants in the presence of a catalyst. Catalysis is, of course, not a necessary condition for an excellent atom economy. Consider the stoichiometric addition of elemental bromine to \(n\)-hexene (Scheme 1). In this situation, all of the reactants are incorporated into the desired brominated compound 3. This transformation is 100% atom economical, independent of the reaction yield.

\[
\text{Atom Economy} = \left( \frac{\text{MW of Product}}{\sum (\text{MW of Reactants})} \right)
\]

**Equation 1.** The atom economy of a given reaction is determined by dividing the molecular weight of the product over the molecular weight(s) of the reactants.

\[
AE = \frac{3_{\text{MW}}}{1_{\text{MW}} + 2_{\text{MW}}} = \frac{243.97}{84.17 + 159.80} = 1.00 \text{ or } 100\%
\]

**Scheme 1.** The bromination of \(n\)-hexene has an atom economy of 100%.

By comparison, in Scheme 2, the reaction of ethyl propionate and methylamine has a low degree of atom economy. In this reaction, the ethoxide group in 4 is substituted for 5 to afford
amide 6; such a reaction generates a significant amount of byproduct. In calculating the atom economy for this reaction (Table 1), approximately 65% of the starting material ends up in the final product. Inferences can be made about the synthesis of 6 based upon the calculations in Table 1: (1) The reaction yield is not taken into account making the AE for this reaction constant regardless of whether the process is low- or high-yielding. (2) The molar excess of reactants is also not taken into account, thus the AE is unaffected if, for example, 1.2 or 9.0 equivalents of 4 are used to make 6. In calculating the atom economy, yields and molar excesses are deliberately ignored and emphasis is exclusively placed on reaction stoichiometry making the calculations reasonably simple.\(^7\)

\[
\text{Scheme 2. The substitution reaction of methyl amine and ethyl propionate offers the desired amide with a low atom economy.}
\]

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Atoms Utilized</th>
<th>Atoms Unutilized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>MW</td>
<td>Empirical Formula</td>
</tr>
<tr>
<td>C(<em>5)H(</em>{10})O(_2)</td>
<td>102.15</td>
<td>C(_3)H(_5)O</td>
</tr>
<tr>
<td>CH(_3)NH(_2)</td>
<td>31.06</td>
<td>CH(_4)N</td>
</tr>
<tr>
<td>Total</td>
<td>C(<em>6)H(</em>{15})NO(_2)</td>
<td>133.21</td>
</tr>
</tbody>
</table>

Therefore, the \(\%\) atom economy = \(\frac{87.13}{133.21}\) = 0.6540 or 65.40%.

Table 1. In the nucleophilic acyl substitution reaction to afford 6, approximately 65% of the reactant mass ends up in the desired product.

Contrary to percent yield, calculated atom economies for sequential reactions cannot be multiplied due to the summation of reactants. Generically, for the formation of product “G” where:
\[ \text{Atom Economy} = \left( \frac{\text{MW of } G}{\text{MW of } A + \text{MW of } B + \text{MW of } D + \text{MW of } F} \right) \]

**Equation 2.** In a stepwise synthesis, the atom economy is determined by dividing the molecular weight of the product by the summation of the molecular weights of the reactants independent of any intermediates.

Intermediates of the preceding generic reaction (i.e. C and E) are ignored in the total calculation of atom economy because they are directly or indirectly formed from A and B, both of which both of which have already been taken into account. The same rule of thought is also applied to a branched synthesis as seen in Figure 1. Intermediates C, H, E and J are ignored in the calculation of atom economy because they derive from starting materials A, B, D, F, G and/or I.

\[ \begin{align*}
A + B & \rightarrow C \\
C + D & \rightarrow E \\
E + F & \rightarrow G \\
D + C & \rightarrow E \\
H & \leftarrow F + G \\
H + I & \leftarrow H + I \\
E + J & \rightarrow P \\
\end{align*} \]

**Figure 1.** A branched, convergent synthesis takes into account all starting reactants required to afford product \( P \) when calculating the atom economy.

The concept of atom economy utilizes certain assumptions to simplify the mathematics. Because AE is a measurement of how much of the reactant mass ends up in the desired product, solvents and reagents (including inorganic salts, quenching agents, and catalysts) are ignored in the calculation.\(^7\) For a given reaction that makes use of a resolution step, the reaction stoichiometry must be adjusted to account for the fact that some portion of the mass will be discarded as the unwanted enantiomer. Thus, AE ultimately depends on reaction stoichiometry.
Historically, the success of a synthesis is primarily measured in terms of yield where every 1 mole of starting material used in a chemical process should ideally afford 1 mole of new product. Thus, the challenge, based on this metric, lies in trying to convert all of the starting material to a desired target independent of the path—where the end justifies the means. Such a metric is not acceptable by the basic principles of green chemistry. The success of a synthetic procedure, when considering the AE of a reaction, is a function of how much starting material ends up in the desired product. An efficient synthesis will incorporate all of the starting materials into the final product independent of yield. Thus, a high yielding reaction is not necessarily efficient and *vice versa*. The inherent challenge for chemists is to develop new processes that are high yielding, produce little to no waste and effectively increase the atom economy for a given reaction.

**A Practical Use of Atom Economy**

Because it is an expression of the percentage of the starting material that ends up in the final product, the reaction AE is often used to compare different synthetic processes. An example of the utility of atom economy in industry is the evolution of the process for producing phenol. It is estimated that 4.5 billion pounds of phenol were produced in the United States in 1995 alone. The earliest processes for synthesizing phenol (Scheme 3) involved sulfonation of benzene to make 9, which upon treatment with sodium hydroxide afforded the desired phenol in high yields. Such a method has an atom economy of 43.53% (Table 2). The remaining 56% of the reactant mass is lost to the formation of sodium bisulfate and water as byproducts.

![Scheme 3. Original processes for synthesizing phenol from benzene.](image-url)
### Table 2. Sulfonation of benzene to synthesize phenol has an atom economy of approximately 44%.

\[
AE = \frac{\text{MW of } C_6H_5O}{\Sigma (\text{MW of } C_6H_6, H_2SO_4, NaOH)} = 0.4353 \text{ or } 43.53\%
\]

In more recent methods, cumene is used as the starting material for producing phenol. In this method (Scheme 4), dry benzene is reacted with propylene in the presence of catalytic AlCl₃ and hydrochloric acid or a zeolitic catalyst under reduced pressure to primarily afford cumene in approximately 95% yield. Other byproducts of this reaction include diisopropyl benzene and heavy aromatics. The cumene is then reacted with molecular oxygen, usually at atmospheric pressure, in the presence of a zeolitic catalyst to create \textbf{13}. The cumene hydroperoxide is then immediately treated with catalytic amounts sulfuric acid thereby giving phenol and acetone—approximately 6 tons of acetone for every 10 tons of phenol. This process has an atom economy of roughly 62% (Table 3), and the remaining 38% is the coproduct acetone, which is typically sold as a solvent. The fact that this process is, by definition, 100% economically efficient makes phenol synthesis via cumene oxidation much more preferred than benzene sulfonation. Interestingly enough, it is estimated that 97% of the 8.9 million tons of phenol produced globally is done so by cumene oxidation.
Scheme 4. The synthesis of phenol and acetone via cumene production from benzene and propene.

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Target</th>
<th>Waste</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>Atoms Utilized</td>
<td>MW</td>
</tr>
<tr>
<td>C₆H₆</td>
<td>C₅H₅</td>
<td>77.11</td>
</tr>
<tr>
<td>C₃H₆</td>
<td>H</td>
<td>1.01</td>
</tr>
<tr>
<td>O₂</td>
<td>O</td>
<td>16.00</td>
</tr>
<tr>
<td>Total</td>
<td>C₆H₁₂O₂</td>
<td>152.21</td>
</tr>
</tbody>
</table>

AE = \( \frac{\text{MW of } C₆H₆O}{\sum (\text{MW of } C₆H₆, C₃H₅, O₂)} \) = 0.6184 or 61.84%

Table 3. Phenol production via cumene oxidation has an atom economy of approximately 62%. The remaining 38% is the coproduct acetone.

In industrial processes, atom economy is a useful metric for determining how much of the starting material ends up in the final product. As is the case in comparing different methods of phenol production, the fact that cumene oxidation is 100% atom economical makes the benzene sulfonation method obsolete. While the “waste” formed in both cases possesses some utility to the chemical industry, acetone and sodium bisulfate are widely used, cumene oxidation is the preferred method.
The Ideal Synthesis

A true test of the utility of the atom economy metric lies in the synthesis of complex molecules. Currently, synthetic organic chemistry is in the midst of a revolution where attempts are being made to synthesize a target molecule using ideal conditions. Clark defined the “ideal synthesis” as one that incorporates a safe, simple, environmentally acceptable, one-step process into achieving a desired product, either natural or designed, in quantitative yield from available starting materials with no wasted reagents.\textsuperscript{11} By this definition, a reaction sequence involving subsequent protection and deprotection steps would be less ideal than an alternate scheme where the use of blocking groups is avoided. In terms of sustainable chemistry, effort should be made to circumvent unnecessary derivatization\textsuperscript{13} as any process that generates a significant amount of waste is atomically uneconomical and therefore does not approach ideal conditions. Interestingly enough, there is no direct correlation between the length of a synthesis and its atom efficiency.\textsuperscript{14,15}

It is generally believed that the ideal synthesis is approached from two perspectives: (1) use of “strategy-level reactions” that significantly increase target-relevant complexity in one step (i.e. Diels-Alder reactions) or (2) use of multi-step processes such as cascade or domino reactions that produce equivalent changes in complexity in one step.\textsuperscript{11} Such processes indirectly attempt to avoid use of excessive steps (i.e. protection/deprotection sequences) and reagents while maximizing yields. As an example (Scheme 5), Langer demonstrated a transition metal-mediated Mukaiyama-aldol cyclization with 1,2-diketones to regioselectively afford substituted cyclopent-2-en-1-ones.\textsuperscript{16} This domino-type transformation affords in modest yields in the presence of 2 equivalents of TiCl\textsubscript{4} and increases the complexity of two seemingly ordinary molecules by introducing a quaternary center stereoselectively. While the yields do not approach unity and the process does not boast an excellent atom economy (approximately 57%), the transformation is closer to being ideal than starting from an expensive, chiral compound or performing a lengthy
stepwise synthesis. An un-ideal approach could afford the same molecule but probably in much lower yields and with a significant amount of waste.

\[
\begin{align*}
\text{Me}_3\text{SiO} & \quad \text{Me}_3\text{SiO} & \quad \text{Me}_3\text{SiO} \\
\text{15} & + & \text{16} \\
\text{TiCl}_4 & \quad \text{DCM, -78 °C} & \quad \text{64%, 9:1} \\
\text{HO} & \quad \text{HO} & \quad \text{HO}
\end{align*}
\]

\[
\text{AE} = \frac{17_{\text{MW}}}{15_{\text{MW}} + 16_{\text{MW}}} = \frac{212.25}{274.56 + 100.13} = 0.5665 \text{ or } 56.65\%
\]

**Scheme 5.** A domino Mukaiyama-aldol cyclization with 1,2-diketones regioselectively affords substituted cyclopent-2-en-1-ones.

**Conclusion**

Atom economy is an important part of sustainable chemistry. Therefore, AE does not embody the concept of sustainable chemistry as a whole. To claim that an atomically economical process is “green” is not entirely correct. A method that boasts a high atom economy may require a large amount of energy to complete, for example. The corollary to this notion is that while future iterations of a given synthesis or synthetic step will almost certainly evolve towards a higher degree of “greenness” over time, they may not be entirely atomically economical. Only an ideal synthesis—high yielding, synthetically terse, highly selective, minimized waste, etc.—truly embodies the concept of sustainable chemistry and, therefore its atom economy. It is the synthetic chemist’s responsibility to steer his or her synthetic route towards the ideal conditions. While pursuit of the ideal synthesis is unlikely to be reached in practice, used as a calibration point, it serves a far better purpose than calibration against past efforts. Atom economy, a metric used to identify the amount of starting material and reactants that end up in the desired product over the course of a synthetic procedure, is one way to measure the idealness of said synthesis.
Atom economy does, however, take into account numerous assumptions. Such suppositions make AE an imperfect tool for gauging the atomic efficiency of a total synthesis. Therefore, these attributes (i.e. yield, workup reagents, etc.) are deliberately left out of the calculation of AE, for the sake of simplicity. While there are numerous alternatives to the atom economy metric, suggestions for alternative metrics are beyond the scope of this abstract, yet will be mentioned in the seminar.

References


