Atom Economy and Yield of Synthesis Sequences

by **Marco Eissen***[a]), **Radoslaw Mazur**[b]), **Heinz-Georg Quebbemann**[c]), and **Karl-Heinz Pennemann**[d])

[a]) Danziger Strasse 25a, D-26419 Schortens (phone, fax: +49446180707;
e-mail: marco.eissen@stud.uni-goettingen.de)
[b]) Institut für Physik der Carl von Ossietzky Universität Oldenburg, D-26111 Oldenburg
[c]) Institut für Mathematik der Carl von Ossietzky Universität Oldenburg, D-26111 Oldenburg
[d]) Department für Informatik der Carl von Ossietzky Universität Oldenburg, D-26111 Oldenburg

To the memory of *Marcus Ratzke*

Atom economy (AE) or *atom utilization* was one of the first defining terms in the sustainable chemistry movement. In contrast to the often-cited twelve (qualitative) principles of green chemistry, AE represents a metric for quantification purposes. The theoretical efficiency of a reaction expressed by its stoichiometric equation can be determined by AE = Product [g/mol]/(Substrate 1 + Substrate 2 + ...) [g/mol] and compared with synthetic alternatives. Of course, the atom economy will be of limited use, if starting materials differ much in complexity, *i.e.*, in the degree of refinement. In these cases, their syntheses have to be taken in consideration, too. But, the further the retrospect goes and the more preceding synthesis steps ramify, the more complex the calculation gets. To overcome this limitation, we introduce a stepwise approach that is enabled by a simple modification of the above formula (P = product; S = substrate; Syn. = synthesis): AE = P [g/mol]/((S1/AE(Syn. of S1)) + (S2/AE(Syn. of S2)) + ...) [g/mol]. To illustrate this equation, which is derived mathematically, the convergent multistep synthesis of the natural product *trans*-chrysanthemic acid is subjected to a stepwise method of calculation. The equation can be understood as a general expression for related ratios, *i.e.*, there are corresponding modified equations for yield, selectivity, *etc.* In terms of the yield, it is no longer necessary to decide between the chains of the convergent synthesis, when possibly forced to ignore significant parts of the sequence. For demonstration purposes, the yield of the convergent synthesis of the natural product peridinin has been determined with a correspondingly modified equation.

Introduction. – The concept of *atom economy* (AE) or *atom utilization* [1–4] has drawn much attention in organic chemistry. While the twelve principles [5] of green chemistry are all qualitative, AE represents a metric that enables the objective comparison of alternatives and, therefore, belongs to the second principle of *Winterton*'s 'Twelve More Principles of Green Chemistry' [6]. The idea of AE reactions helps to promote thinking in the direction of sustainable chemistry [7]. High AE, *i.e.*, when the ratio of pseroduct to substrates[1]) due to the stoichiometric

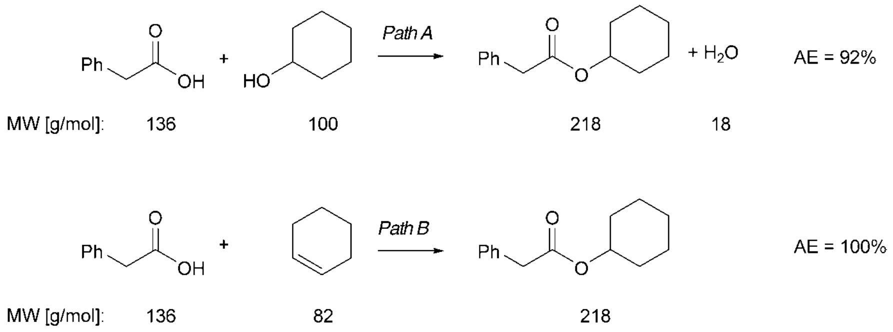
---

[1]) In terms of the result, it does not make any difference whether we refer with *product* to all of the products or to all of the substrates of the synthesis. But, there is a difference whether the ratio of the number of atoms is considered or the ratio of the molecular weights. Because the latter takes into account to a higher degree the resource requirements, we perform a mass balance rather than an atom balance, concerning stoichiometry and reverting to *Trosts*' concept.

equation2) is close to 100%, i regarded as high synthetic efficiency, and the product contains most or ven all of the atoms of the substrates – only a little or none of the substrate is wasted. However, it is a concept with severe limitations, the most obvious of which is its failure to take into account incomplete conversion of substrates, reaction auxiliaries such as catalysts and solvents, and workup auxiliaries. AE is, thus, merely a mass-related expression of the stoichiometric equation AE = Product [g/mol]/(Substrate 1 + Substrate 2 + ...) [g/mol]. The quality of reactants and of waste, *e.g.*, substance properties such as toxicity, is *not* considered. The application of simple metrics, *e.g.*, mass index and other measures, taking into account chemical yield, reaction as well as workup auxiliaries, or reactant and waste properties, can be found in the literature [9]. Comments regarding the relevance of AE compared to mass index and other metrics are given in this reference and elsewhere [7][10]. This contribution will not elaborate on this topic.

To start with an example, *Scheme 1* shows two types of esterification reactions for the synthesis of a cyclohexyl ester. In case of 1,2-addition to cyclohexane (*Path B*), formation of H_2O can be avoided, and, therefore, the AE can be raised to 100%. Of course, in general, esterification with cyclohexanol (*Path A*) is not problematic, and the AE of 92% is still very good – especially when compared with other reactions.

Scheme 1. *Atom Economy of the Esterification of Phenylacetic Acid with Different Substrates* [11]



In contrast, the methylenation of carbonyl compounds *via* the *Wittig* reaction, generates 1 equiv. of triphenylphospine oxide ($Ph_3P=O$) per equiv. of methylene group transferred, so AE gets worse the smaller the carbonyl molecule is. It is clear that an advantage of *B* over *A* (*Scheme 1*) exists only when cyclohexene is *not* made from

---

2) Because, sometimes, there is not a clear agreement about the term *stoichiometric equation*, we would like to define how it is used throughout the text. Stoichiometry and stoichiometric coefficients, respectively, are considered as the theoretical relationship that exists in chemical formulae of the intended chemical reaction, *i.e.*, as a mol-to-mol problem of substrates, product, and coupled products. This means that incomplete conversion of the substrates to the desired product, *i.e.*, the occurrence of undesired side reactions resulting in by-product formation and decrease in yield, is ignored. (Note the difference in the meaning of *coupled product* and *by-product*.) If yield and substrate excess are to be considered, another metric, the selectivity S = Product [kg]/(Substrate 1 + Substrate 2 + ...) [kg], must be considered. As already mentioned in the abstract, the procedure outlined in this article can also be applied to this metric. Nevertheless, in principle, of course, it is possible to set up a stoichiometric equation that includes substrate excess and by-product formation, in case a mass balance is given. Even bacteria growth in biotechnological applications can be considered, as outlined in [8].

cyclohexanol, *e.g.*, *via* dehydration. This train of thought poses the question about the history of the substrates. Especially when the starting material differs much in complexity, the significance of the AE of a single synthesis compared to an alternative one is limited. Obviously, to obtain more-reliable conclusions, it will be necessary to 'integrate' the synthesis sequences leading to the substrates used into the examination of the final synthesis step. To generalize the question, a universal complex [12][13] synthesis tree [14] is given in the *Figure*.

For a synthesis chain, the yields of each step have to be multiplied together to obtain the overall yield. However, this procedure cannot be transferred to the AE. The reason for this is that the yield relates the product only to a single substrate directly resulting from a previous synthesis, while AE includes all of the substrates. Therefore, the product has to be related to all substrates involved in the whole sequence. As a consequence, every substrate in the denominator of the AE of, *e.g.*, *Step n* (*Alternative 2* in the *Figure*) has to be replaced by the substrates of the preceding steps. It is important to take into account the stoichiometric coefficients of these intermediates. The number of synthesis steps may prevent an easy determination of the AE of a synthesis sequence. In addition, potentially emerging multiplicities of stoichiometric coefficients unequal to 1 may also contribute negatively. And, even worse, in a synthesis design, there are several different sequences that need to be considered and compared. Therefore, a method is required that allows a successive procedure, without inclusion of the complex sequence in its totality. An expression is needed – generally formulated – with which the AE of n successive steps, AE $(1,\ldots,n)$, can be determined, wherein, *e.g.*, substrate 1 in the last step n results from a previous step $n-1$ and, therefore, represents an intermediate.

In the following approach, the derivation of an appropriate formula is given. Its easy application is exemplified by the determination of the AE of the convergent synthesis of *trans*-chrysanthemic acid. In terms of the most-elementary chemical metric, *i.e.*, the yield, we determined the overall yield of the convergent synthesis of peridinin by way of an example. For this, we used a corresponding, but slightly modified formula.

Derivation. – The known expression for the AE of a single, independent synthesis is:

$$\mathrm{AE}(1) = \frac{b_{\mathrm{product}} \cdot \mathrm{MW}_{\mathrm{product}}}{a_{\mathrm{substr.1}} \cdot \mathrm{MW}_{\mathrm{substr.1}} + \ldots + a_{\mathrm{substr.}m} \cdot \mathrm{MW}_{\mathrm{substr.}m}}, \tag{1}$$

where the coefficients a and b denote the multiplicity with which a molecule enters or leaves the synthesis, resp.; MW means molecular weight. Now, the following formula expresses the atom economy for a sequence of n successive syntheses, if, say, substrate 1 at the last stage is the product at stage $n-1$:

$$\mathrm{AE}(1,\ldots,n) = \frac{b_{\mathrm{product}} \cdot \mathrm{MW}_{\mathrm{product}}}{\frac{a_{\mathrm{substr.1}} \cdot \mathrm{MW}_{\mathrm{substr.1}}}{\mathrm{AE}(1,\ldots,n-1)} + \sum_{j=2}^{m} a_{\mathrm{substr.}j} \cdot \mathrm{MW}_{\mathrm{substr.}j}}. \tag{2}$$

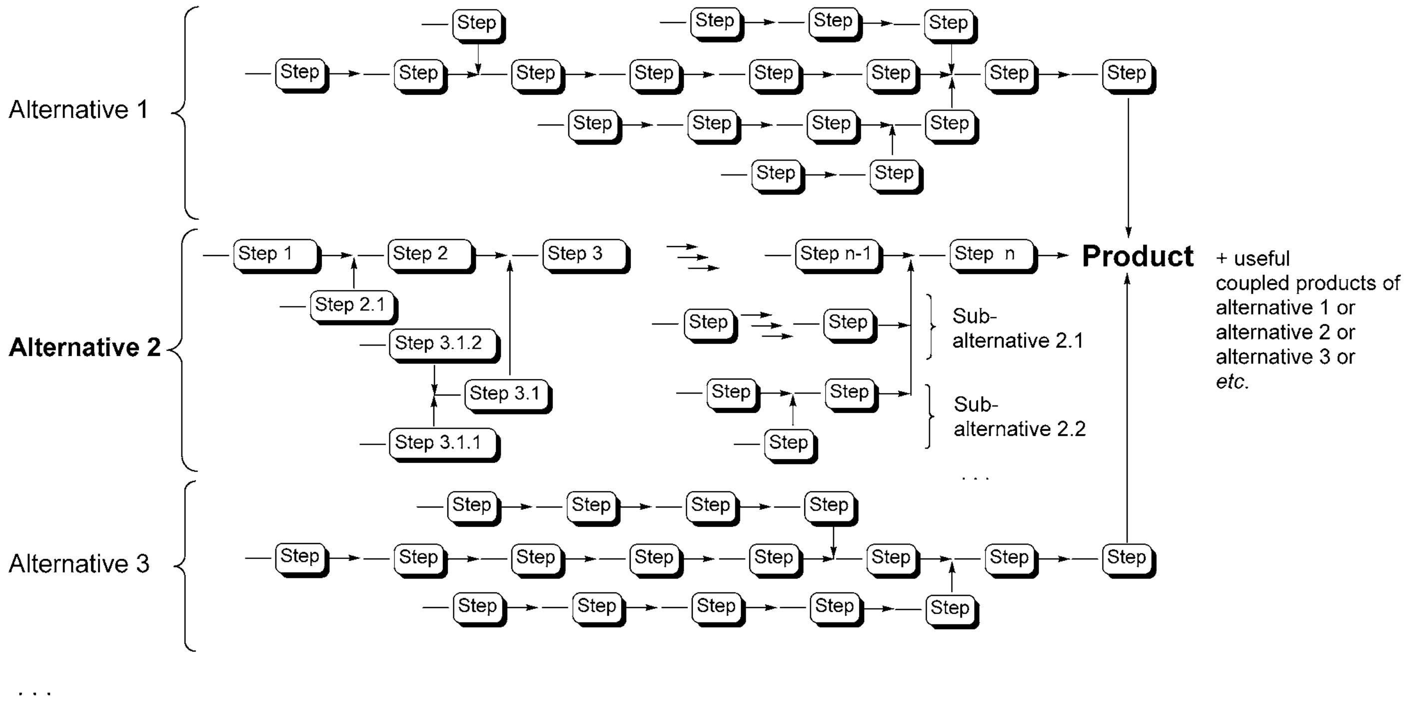


Figure. *Different synthesis sequences to obtain a product*. Alternatives themselves in turn include subalternatives.

To rationalize this formula, we first consider the case $n=2$. The general stoichiometric equation for synthesis i, with product $p(i)$, is:

$$\sum_s a_s(i) \cdot \mathrm{MW}_s = b(i) \cdot \mathrm{MW}_{p(i)} + \sum_q b_q(i)\mathrm{MW}_q\,,$$

where s and q denote the substrates and coupled products, respectively; in $b(i)$, the index $p(i)$ has been omitted. Combining now the stoichiometric equations for $i=1$ and $i=2$, and using 'prime' notation for molecules from synthesis 1 (in particular $p'=p(1)$), we obtain:

$$\sum_{s \neq p'} a_s(2) \cdot \mathrm{MW}_s + \frac{a_{p'} \cdot (2)}{b(1)} \sum_{s'} a_{s'}(1)\mathrm{MW}_{s'} = b(2) \cdot \mathrm{MW}_{p(2)}$$

$$+ \sum_q b_q(2)\mathrm{MW}_q + \frac{a_{p'}(2)}{b(1)} \sum_{q'} b_{q'}(1)\mathrm{MW}_{q'}.$$

Therefore, assuming that $p(2)$ is different from all q', we should obtain:

$$\mathrm{AE}(1,2) = \frac{b(2) \cdot \mathrm{MW}_{p(2)}}{\sum\limits_{s \neq p'} a_s(2) \cdot \mathrm{MW}_s + \frac{a_{p'}(2)}{b(1)} \sum\limits_{s'} a_{s'}(1) \cdot \mathrm{MW}_{s'}}.$$

According to *Eqn. 1*, the second part of the denominator is $a_{p'}\,(2) \cdot \mathrm{MW}_{p'}/\mathrm{AE}(1)$, thus, this equation coincides with *Eqn. 2* for $n=2$. Continuing by mathematical induction, we then use *Eqn. 2* to define AE (1, ..., n) for any n.

Results. – According to the preceding section, the AE of a sequence of n synthesis steps can be calculated by *Eqn. 2*, *i.e.*, in another formulation by:

$$\mathrm{AE}(1,\ldots,n) = \frac{coef_{\mathrm{product}} \cdot \mathrm{MW}_{\mathrm{product}}}{\frac{coef_{\mathrm{substr.1}} \cdot \mathrm{MW}_{\mathrm{substrate1}}}{\mathrm{AE}(1,\ldots,n-1)} + coef_{\mathrm{substr.2}} \cdot \mathrm{MW}_{\mathrm{substrate\ 2}} + \ldots + coef_{\mathrm{substr.}m} \cdot \mathrm{MW}_{\mathrm{substrate}\ m}}.$$

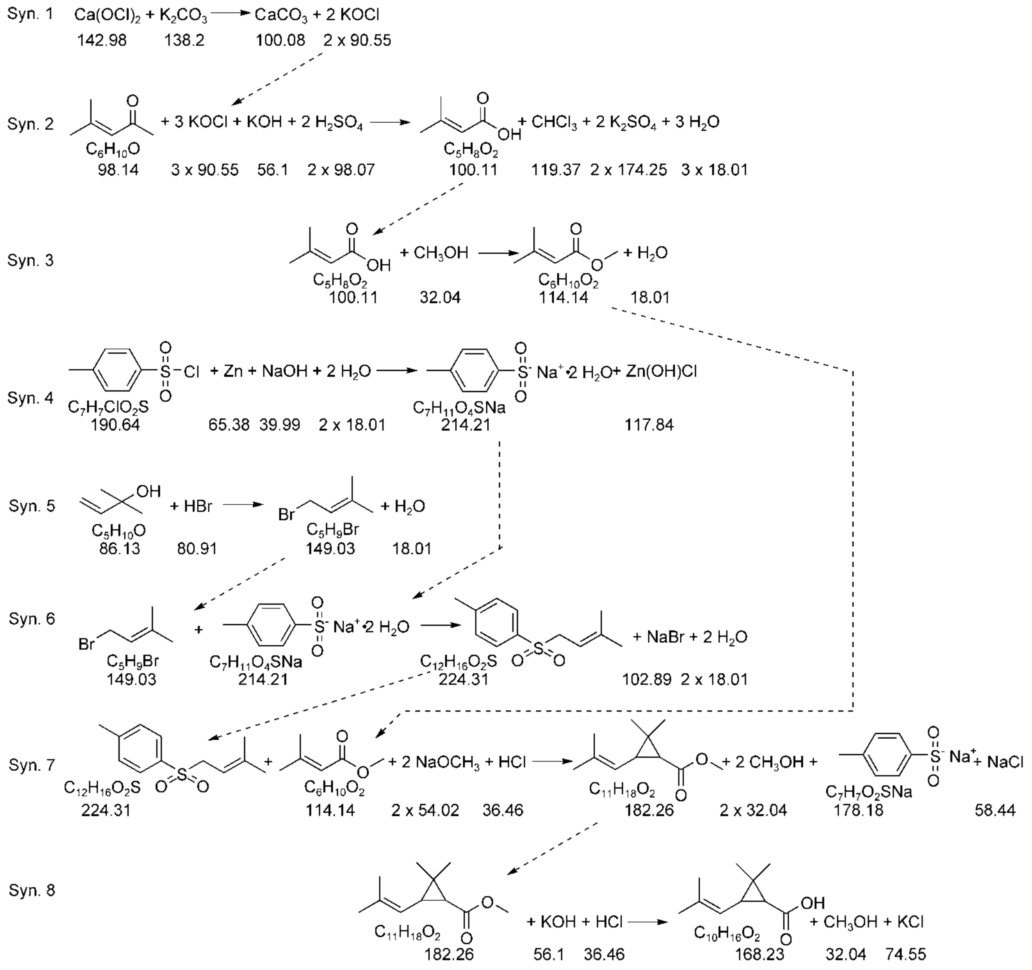
Compared to the known expression of the AE for a single synthesis step (*Eqn. 1*), it can be concluded that a substrate whose history shall be considered has to be divided by the underlying AE. More generally, substrates 2 to m can also be considered as intermediates of different reaction paths, and then, *Eqn. 3*, which corresponds to the second formula given in the *Abstract*, may be used for the AE of the entire synthesis sequence.

$$\mathrm{AE}(1,\ldots,n) = \frac{coef_{\mathrm{product}} \cdot \mathrm{MW}_{\mathrm{product}}}{\frac{coef_{\mathrm{substr.1}} \cdot \mathrm{MW}_{\mathrm{substrate\ 1}}}{\mathrm{AE}(1,\ldots,n-1)} + \frac{coef_{\mathrm{substr.2}} \cdot \mathrm{MW}_{\mathrm{substrate\ 2}}}{\mathrm{AE}(\text{sequence to substrate 2})} + \ldots + \frac{coef_{\mathrm{substr.}m} \cdot \mathrm{MW}_{\mathrm{substrate}\ m}}{\mathrm{AE}(\text{sequence to substrate } m)} \tag{3}$$

As this equation is also valid for all steps before synthesis n, the AE atom of a complex synthesis sequence (*Figure*) can be calculated in a stepwise procedure.

In the following section, the idea of *Eqn. 2* is applied to two convergent syntheses of natural products, *trans*-chrysanthemic acid (*Scheme 2*) and peridinin (*Scheme 3*). In the first example, we demonstrate how AE of a sequence can be easily determined with *Eqn. 2*; the equation that has to be set up in a general manner is also given. In the second example, the overall yield is calculated by a slightly modified equation, (see *Eqns. 13* and *14*).

Scheme 2. *Possible Synthesis Sequence of* trans-*Chrysanthemic Acid* [15]. For a review, see [16].



Example 1: Atom Economy for the Synthesis of trans-*Chrysanthemic Acid.* The AE of the first three steps, Syn. 1, Syn. 2 and Syn. 3 (*Scheme 2*), including each previous one, is calculated in the usual manner:

$$\mathrm{AE(Syn.1)} = \frac{2 \cdot 90.55}{142.98 + 138.2} = 64.4\%, \tag{4}$$

$$\mathrm{AE(Syn.1, Syn.2)} = \frac{100.11}{98.14 + {}^{3}\!/_{2}(142.98 + 138.2) + 56.1 + 2 \cdot 98.07} = 13.0\%, \tag{5}$$

$$\begin{aligned}\mathrm{AE(Syn.1, ..., Syn.3)} &= \frac{114.14}{98.14 + {}^{3}\!/_{2}(142.98 + 138.2) + 56.1 + 2 \cdot 98.07 + 32.04} \\ &= 14.2\%. \end{aligned} \tag{6}$$

Utilization of *Eqn. 2* provides the same results:

$$\mathrm{AE(Syn.1, Syn.2)} = \frac{100.11}{98.14 + \dfrac{3 \cdot 90.55}{\mathrm{AE(Syn.1)[=0.644]}} + 56.1 + 2 \cdot 98.07} = 13.0\%, \tag{7}$$

$$\mathrm{AE(Syn.1, ..., Syn.3)} = \frac{114.14}{\dfrac{100.11}{\mathrm{AE(Syn.1,Syn.2)[=0.13]}} + 32.04} = 14.2\%. \tag{8}$$

Analogously, the AE of steps 4–6, whose calculation is not shown here, is obtained with 44.9%. The integration of both paths, Syn.1–Syn.3, and Syn.4–Syn.6, provides AE(Syn.1–Syn.7):

$$\mathrm{AE(Syn.1, ..., Syn.7)} =$$

$$\frac{182.26}{\dfrac{224.31}{AE(Syn.4,...,Syn.6)[0.449]} + \dfrac{114.14}{AE(Syn.1,...,Syn.3)[=0.142]} + 2 \cdot 54.02 + 36.46} = 12.6\% \tag{9}$$

Including the last synthesis step, Syn.8, one obtains:

$$\mathrm{AE(Syn.1, ..., Syn.8)} = \frac{168.23}{\frac{182.26}{\mathrm{AE(Syn.1,...,Syn.7)[=0.126]}} + 56.1 + 36.46} = 10.9\%. \tag{10}$$

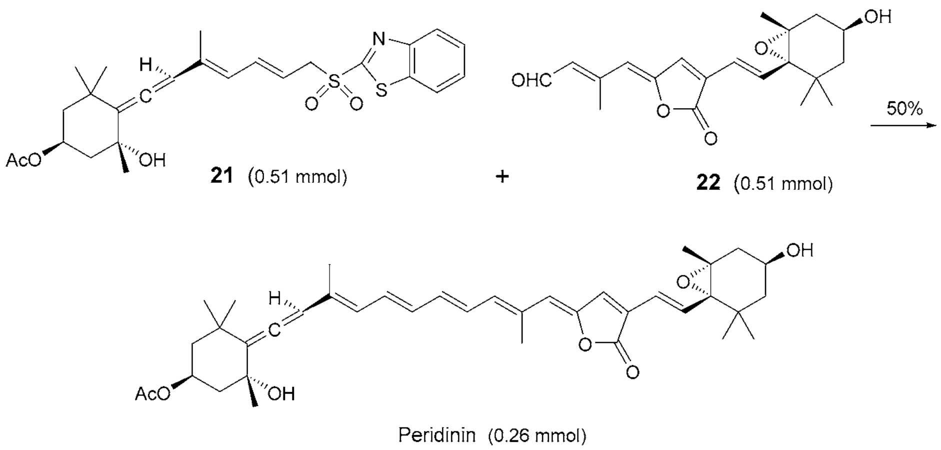
The determination of AE(Syn.1–Syn.8) in the usual manner has to occur in one calculation step (*Eqn. 11*), with the same result as in *Eqn. 10.* All substrates are related to the product:

$$\begin{aligned}\mathrm{AE}(\mathrm{Syn.1},\ldots,\mathrm{Syn.8}) = 168.23/[98.14 + 3/2(142.98 + 138.2) + 56.1 + 2\cdot 98.07\\ + 32.04 + 190.64 + 65.38 + 39.99 + 2\cdot 18.01 + 86.13 + 80.91 + 2\cdot 54.02 + 36.46\\ + 56.1 + 36.46] = 10.9\% \qquad (11)\end{aligned}$$

The above example also calls attention to the observation that the AE does not necessarily decline with increasing length of the synthesis. Whereas AE in *Eqn. 5* is 13%, it is 14.2% in *Eqn. 6*. At first glance, this finding contradicts what one would normally expect. But, a thought experiment provides clarity. Assuming a product with a MW of 200 g/mol is made from substrates whose molecular weights add up to 400 g/mol, we have an AE of 50% in this reaction step. If, in a second reaction, a molecule of 600 g/mol is added *via* an addition reaction, *i.e.*, no coupled products are formed, then the overall AE amounts to 80% ((200 + 600)/(400 + 600)).

Example 2: Overall Yield for the Synthesis of Peridinin. Normally, to determine the yield of a convergent synthesis, it is necessary to select a certain reaction chain. In the case of the synthesis of peridinin (*Scheme 3*), one has to decide between *Paths C* or *D* (*Scheme 4*)[3]) to calculate the overall yield. This means that either *D* or *C* will be excluded from the determination of the overall yield.

Scheme 3. *Final Step of the Synthesis of Peridinin* [17]. The yield is relative to **21** (see *Scheme 4*).



21 (0.51 mmol) + **22** (0.51 mmol)

Peridinin (0.26 mmol)

Normally, only a single path is considered to calculate the overall yield of a sequence. Therefore, the question arises how a second chain can be integrated into the determination of the yield. First, it is necessary to clarify how to relate the yield to more than one substrate at all. To extend the normal calculation (*Eqn. 12*), the number of substrates (in *Scheme 3*, **21** and **22**) has to be considered, and the equation has to be modified by a corresponding factor (in the above example, it is 1/2, because two substrates with a stoichiometric coefficient of 1 are considered (*Eqn. 13*)).

---

[3]) For specifications of compounds **2**–**18**, see [17].

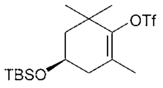
Scheme 4. *Syntheses of the Peridinin Precursors* **21** *and* **22** (see *Scheme 3*). The yields obtained in each step are indicated. As **22** has not been isolated, a yield of 100% was assumed.

Path C: Overall yield (**21**): 17.4%

$$\mathbf{5} \xrightarrow{97\%,\ 87\%} \mathbf{6} \xrightarrow{99\%} \mathbf{7} \xrightarrow{100\%} \mathbf{4} \xrightarrow{53\%} \mathbf{8} \xrightarrow{84\%} \mathbf{9} \xrightarrow{80\%} \mathbf{10} \xrightarrow{86\%,\ 98\%} \mathbf{2} \xrightarrow{78\%,\ 89\%} \mathbf{21}$$

Path D: Overall yield (**22**): 15.9%

$$\mathbf{5} \xrightarrow{97\%,\ 87\%} \mathbf{6} \xrightarrow{99\%} \mathbf{7} \xrightarrow{100\%} \mathbf{4} \xrightarrow{77\%} \mathbf{15} \xrightarrow{70\%} \mathbf{16} \xrightarrow{89\%} \mathbf{17} \xrightarrow{81\%} \mathbf{18} \xrightarrow{49\%} \mathbf{3} \xrightarrow{100\%} \mathbf{22}$$



5

TBS = ^{t}BuMe$_2$Si
Tf = F$_3$CSO$_2$

$$\text{Yield(Peridinin)} = \frac{0.26\,\text{mmol}}{0.51\,\text{mmol}} = 50\% \tag{12}$$

$$\text{Yield(Peridinin)} = \frac{0.26\,\text{mmol}}{\frac{1}{2}\cdot(0.51\,\text{mmol} + 0.51\,\text{mmol})} = 50\% \tag{13}$$

This arithmetic averaging does not influence the yield (50%), which merely would have been changed if the substrate additionally considered had been used in excess. Of course, normally, one or more substrates are used in excess to foster the completeness of key substrate conversion, which often is much more expensive than the other substrates. But, the example chosen (equimolar ratio) elucidates that this procedure makes sense.

Remembering the perception in terms of the AE (compare *Eqn. 2*), the results of both reaction chains *C* and *D* in *Scheme 4* can be incorporated into an expression for the overall yield of peridinin (*Eqn. 14*):

$$\text{Yield(Peridinin)} = \frac{0.26\,\text{mmol}}{\frac{1}{2}\cdot\left(\frac{0.51\,\text{mmol}}{0.174} + \frac{0.51\,\text{mmol}}{0.159}\right)} = 8.5\%. \tag{14}$$

Of course, every side chain belonging to *Paths C* and *D* may similarly be considered as well, if desired.

Discussion. – Normally, when the AE is used to highlight synthetic efficiency, only a single synthesis is considered. In this article, the need to reflect on the history of substrates used in the determination of the AE was exemplified by two different syntheses of cyclohexyl phenylacetate (*Scheme 1*). The more-complex example of the synthesis sequence to *trans*-chrysanthemic acid (*Scheme 2*) illustrates the need for a method to simplify the calculation of the AE for potential alternatives in synthesis design. A problem may arise as a consequence of recording all substrates of all syntheses, which can lead to a false result. Another source of error consists of stoichiometric coefficients $\neq 1$. Whereas 2 equiv. of KOCl result from Syn.1 of the chrysanthemic acid production (*Scheme 2*), 3 equiv. are entered in Syn.2. Therefore, the molecular weights of the substrates needed to produce KOCl cannot be written into the denominator like the others in *Eqn. 11.* Their contributions to the overall AE result from the consideration of the corresponding factor 3/2. By *Eqn. 2* (or *Eqn. 3*), an approach is made that puts aside the need for a complete overview and, instead, allows a stepwise calculation. Normally, when AE of alternative synthesis sequences (that probably even include subalternatives; *Figure*) are to be determined, a calculation of the type of *Eqn. 11* has to be performed each time. But, usually, many addends in the denominator of these equations remain identical in (sub)alternatives to be investigated, because, often, merely parts of the synthesis tree change. Therefore, it appears to be smarter to avoid repeating identical calculations and rather to integrate only those alternative synthesis sequences into further calculations that are actually new. By means of the procedure described herein, the AE of a synthesis-tree fragment can be calculated and integrated into different alternative synthesis scenarios (*Figure*) to be calculated. In *Eqn. 9*, for example, the AE for the steps 1–3 was simply inserted. This pocket-calculator-compatible procedure can be programmed on a computer.

Normally, the AE gets worse the longer the sequence is, but see the principal restriction of this proposition at the end of *Example 1.* Therefore, it appears to be reasonable to start with raw materials that will not have to be built up intricately from small building blocks. The synthetic power of nature, which reverts to solar energy, CO_2 and H_2O, provides us with highly structured products through (almost) no intervention of man's own [18][19]. Thus, renewable resources may contribute to direct chemical research efforts close to *Wender*'s ideal synthesis [20]. It is true that the atom efficiency of the stoichiometric equation finally does not correlate [7] with the mass efficiency of the whole synthesis. AE and other mass-related metrics, such as yield, reaction mass efficiency, and mass intensity, have been examined with regard to their 'greenness' and costs [10]. In their commentary on this reference, *Laird et al.* [21] emphasize the importance of a concentration term, which is, for instance, given with the mass intensity or mass index. Solvents, auxiliary materials, substrate excess, byproduct formation, *etc.*, affect the mass efficiency, as demonstrated by means of, *e.g.*, *Friedel–Crafts* acylation [9], hydrogenation [22], aldol condensation [23] and *Michael* reactions [23]. Compared to the reflection on the AE, the sustainable character of a comparison of synthesis alternatives is better described when considering a full mass balance, expenses, hazards, and environmental concerns [9]. However, AE allows a first rough quantitative assessment for synthesis design. Good chemists want to make good chemistry. The more synthesis steps are involved, the more complex the synthesis tree [14] grows, the more relevant the preview gets to avoid loosing track.

Besides AE, chemical yield can also be subjected to a similar formula to integrate side paths of a synthesis sequence into the determination of an overall yield. By this, one is not forced to concentrate on a certain chain of the sequence, as done hitherto, and to exclude significant parts of the synthesis strategy. The synthesis of peridinin (*Scheme 3*) was presented to give an example, which was chosen because the same amounts of substrates in *Scheme 3* and the similar yields for Paths *C* and *D* in *Scheme 4* facilitate the understanding of the modification of *Eqn. 2* (see *Eqn. 13* and *14*). As a consequence in this special example, the yield of the overall synthesis sequence, of course, does not differ very much from that where only one chain had been considered. With regard to triviality, it appears noteworthy that the yield of ramified synthesis sequences has not always been determined by the outlined procedure.

Conclusions. – Metrics like AE are very useful for quantification purposes, allowing a more objective comparison of alternatives [7][24], especially when all masses (*Winterton*'s 3rd principle [6]) and properties, *e.g.*, toxicity, are considered for a given synthesis [9][25][26]. (For more-holistic approaches, see *Factor 10*, *LCA*, '*rucksack*', *etc.* [27].) The synthesis at the end of a sequence represents only a part of the overall picture of the production of a chemical compound. Therefore, it is important to backtrack the sequence to include the history of the substrates. Herein, we have developed useful formulae (*Eqns. 2* and *3*) for the stepwise calculation of the AE of multi-step syntheses to circumvent the necessity to record all substrates of the sequence in their entity. Similar expressions are valid for the same procedure for the calculation of yield, selectivity, and other characteristics of synthesis sequences. The formula has been derived mathematically and exemplified with the convergent synthesis of *trans*-chrysanthemic acid. We implemented this metric as one among others in our computer software EATOS (Environmental Assessment Tool for Organic Syntheses) [9][25][26], which can also consider useful coupled products (*Figure*) by their comprehension ('Verbund'-like [28]) in the numerator of the formulae. We have also shown how to determine, in an analogous manner, the overall yield of the convergent synthesis of peridinin (*Schemes 3* and *4*).

M. E. thanks the *Deutsche Bundesstiftung Umwelt* for support within the framework of the scholarship program.

REFERENCES

[1] B. M. Trost, *Science* **1991**, *254*, 1471.
[2] R. A. Sheldon, *Chem. Ind. (London)* **1992**, 903.
[3] R. A. Sheldon, *CHEMTECH* **1994**, *3*, 38.
[4] B. M. Trost, *Angew. Chem., Int. Ed.* **1995**, *34*, 259.
[5] P. T. Anastas, J. C. Warner, 'Green Chemistry: Theory and Practice', Oxford University Press, Oxford, 1998, p. 30.
[6] N. Winterton, *Green Chem.* **2001**, *3*, G73.
[7] A. D. Curzons, D. J. C. Constable, D. N. Mortimer, V. L. Cunningham, *Green Chem.* **2001**, *3*, 1.
[8] H. W. Blanch, D. S. Clark, 'Biochemical Engineering', Marcel Dekker, Inc., New York, Basel, 1996, p. 162–180.
[9] M. Eissen, J. O. Metzger, *Chem.–Eur. J.* **2002**, *8*, 3580.
[10] D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.* **2002**, *4*, 521.
[11] G. D. Yadav, P. K. Goel, *Green Chem.* **2000**, *2*, 71.
[12] S. H. Bertz, *New J. Chem* **2003**, *27*, 870.
[13] S. H. Bertz, T. J. Sommer, *Chem. Commun.* **2003**, 1000.
[14] J. B. Hendrickson, *CHEMTECH* **1998**, *28*, 35.
[15] L. F. Tietze, T. Eicher, 'Reaktionen und Synthesen', 2nd edn., Georg Thieme Verlag, Stuttgart, New York, 1991.
[16] S. Jeanmart, *Aust. J. Chem.* **2003**, *56*, 559.

[17] N. Furuichi, H. Hara, T. Osaki, H. Mori, S. Katsumura, *Angew. Chem., Int. Ed.* **2002**, *41*, 1023.

[18] J. O. Metzger, M. Eissen, *Compte Rendus – Chimie* **2004**, in press.

[19] J. O. Metzger, *Nachr. Chem.* **2003**, *51*, 458.

[20] P. A. Wender, *Chem. Rev.* **1996**, *96*, 1.

[21] T. Laird, S. A. Hermitage, U. Tilstam, *Org. Process Res. Dev.* **2003**, *7*, 124.

[22] H.-U. Blaser, M. Eissen, P. F. Fauquex, K. Hungerbühler, E. Schmidt, G. Sedelmeier, M. Studer, in 'Large-Scale Asymmetric Catalysis', Eds. H.-U. Blaser, E. Schmidt, Wiley-VCH, Weinheim, 2003, p. 91–104.

[23] M. Eissen, K. Hungerbühler, S. Dirks, J. O. Metzger, *Green Chem.* **2003**, *5*, G25.

[24] 'Industrial Environmental Performance Metrics: Challenges and Opportunities', Ed. Commitee on Industrial Environmental Performance Metrics, National Academy of Engineering, National Research Council, National Academy Press, Washington, D.C., 1999, p. 85–105.

[25] M. Eissen, J. O. Metzger, E. Schmidt, U. Schneidewind, *Angew. Chem., Int. Ed.* **2002**, *41*, 414.

[26] M. Eissen, 'Bewertung der Umweltverträglichkeit organisch-chemischer Synthesen', BIS-Verlag, Oldenburg, 2001.

[27] K.-H. Robèrt, B. Schmidt-Bleek, J. Aloisi de Larderel, G. Basile, J. L. Jansen, R. Kuehr, P. Price Thomas, M. Suzuki, P. Hawken, M. Wackernagel, *J. Cleaner Prod.* **2002**, *10*, 197.

[28] www.basf.de/en/corporate/innovationen/fakten/chemikalien/verbund/.

Received September 3, 2003