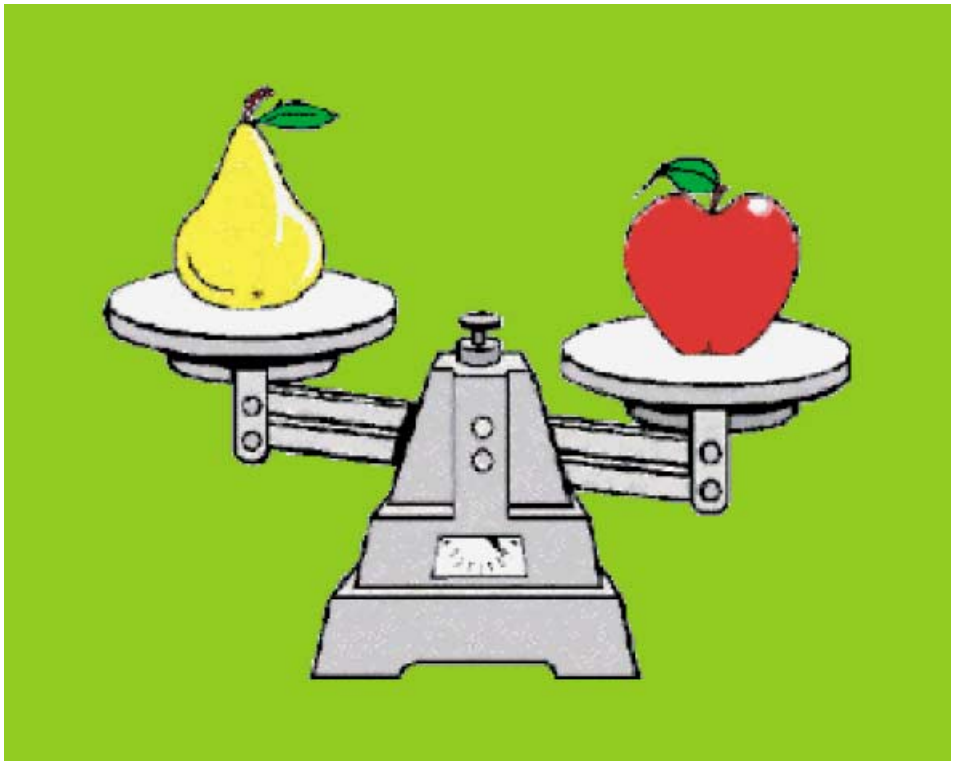

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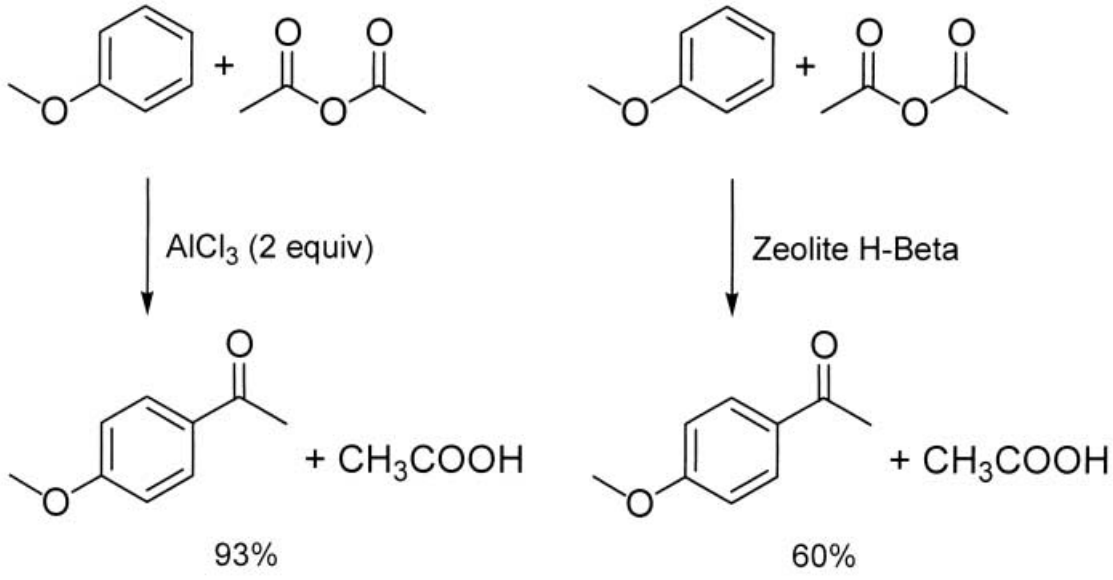

Which alternative is "greener"?

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Environmental Performance Metrics for Daily Use in Synthetic Chemistry

Marco Eissen[a] and Jürgen O. Metzger*[b]

Dedicated to Professor Dietrich Döpp on the occasion of his 65th birthday

Abstract: A simple quantitative approach to enable chemists to compare alternative chemical syntheses on the lab bench with respect to their resource usage and their potential environmental impact is proposed; this may be useful for the systematic design of more sustainable processes. We consider as metrics the mass index S^{-1} and the environmental factor E to characterize quantitatively the reaction input and output, respectively. The potential environmental impact is estimated by using easily available data of each compound of the feed and of each compound of the waste. The calculations can easily be performed using EATOS—environmental assessment tool for organic syntheses.

Keywords: acylation · environmental chemistry · green chemistry · sustainable development · waste prevention

Introduction

Sustainable development has become the key ideal of the new century.[1a] Conservation and management of the resources for development is the most important aspect.[1b] "To achieve sustainable development and a higher quality of life for all people, States should reduce and eliminate unsustainable patterns of production." (Principle 8 of the Rio Declaration) "The sciences should continue to play an increasing role in providing for an improvement in the efficiency of resource utilization and in finding new development practices, resources, and alternatives. There is a need for the sciences constantly to reassess and promote less intensive trends in resource utilization, including less intensive utilization of energy in industry, agriculture, and transportation. Thus, the sciences are increasingly being understood as an essential component in the search for feasible pathways towards sustainable development." (Agenda 21, Chapter 35.2) Lubchenco proposed a new social contract for science representing a commitment on the part of all scientists to devote their energies and talents to the most pressing problems of the day, in proportion to their importance, in exchange for public funding,[2] and a new field of sustainability science is emerging.[3]

Chemistry has an important role to play in achieving a sustainable development,[4–6] and chemists must take a lead in developing the technological dimension of a sustainable civilization[7] and are becoming increasingly aware of the need to meet this challenge. "Green chemistry", "sustainable chemistry", "clean chemistry", "environmentally benign chemistry", and other synonyms for the same approach find increasing attention all over the world, as researchers realize their investigations can potentially contribute to the development of a more benign synthetic chemistry.[8] However, what is a "green" etc. chemical reaction? Anastas proposed a set of qualitative principles that are often used more or less selectively to postulate a reaction to be environmentally benign.[9] For example, Yamamoto et al. described the esterification of carboxylic acids with equimolar amounts of alcohols catalyzed by hafnium(IV) salts and azeotropic removal of the equivalent of water formed with toluene during the reaction as a more environmentally benign alternative to well-known processes,[10] and Xiang et al. reported the fluoroalkyldistannoxane-catalyzed biphasic transesterification in a stainless-steel pressure bottle at 150 °C for 16 h as a "green chemical process".[11] However, why should these syntheses be environmentally more benign and "greener" than, for example, the respective textbook reactions that make use of simple sulfuric acid and sodium hydroxide, respectively, as a catalyst? Evidently, though qualitative criteria may be important, they are not sufficient. Therefore, referring to the principles of Anastas,[9] Winterton proposed "twelve more green chemistry principles", which include the necessity of quantification.[12] A

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simple quantitative approach to enable chemists to compare alternative chemical processes on the lab bench with respect to their resource usage and their potential environmental impact would be of great importance for the systematic design of more sustainable processes.[13] The idea of atom economical reactions[14] may be a useful concept in helping promote thinking in the direction of sustainable chemistry; however, there is no correlation between atom economy, which is solely based on the stoichiometric equation of the reaction, and the critical mass intensity metric, which is based on the actual process considering yield and all materials used in reaction including solvents, auxiliaries for reaction, and workup etc. (vide infra).[15]

Environmental performance metrics in chemical manufacturing and for chemical products within the chemical industry is increasing. Resource-related metrics, such as material intensity, energy intensity, and packaging, as well as environmental-burden metrics, such as environmental incidents and toxic dispersions, are being used.[16] The Environmental Proctection Agency (EPA) has developed a "Green Chemistry Expert System" containing the "Synthetic Methodology Assessment for Reduction Techniques" module that allows the analysis of the amount of chemical waste produced by a manufacturing process.[17] Sheldon proposed the use of the environmental quotient $EQ = E \cdot Q$ when evaluating alternative reaction routes to a product.[18] The environmental factor E characterizes the amount of waste produced per unit amount of product, and Q characterizes the "environmental unfriendliness" or the specific environmental burden of the produced waste. Thus, both the amount and the nature of the waste should be considered. There have been a few papers dealing with the application of the Sheldon approach.[19–23] Hungerbühler developed a methodology to derive equivalents for E and Q for the assessment of fine chemical process alternatives early during their development.[20]

The above-mentioned methods suffer from not having a simple calculation basis and, therefore, are not applicable to chemical syntheses and reactions on a laboratory scale.

Results and Discussion

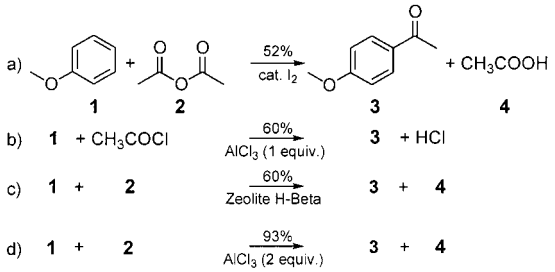
We have been developing a simple, easy to use environmental performance metric to evaluate chemical syntheses and reactions on a laboratory scale in a very practical approach by using EATOS—environmental assessment tool for organic syntheses[24]—to answer the question: "So you think your process is green, how do you know?".[15] This method enables an easy comparison of different chemical reactions giving the same product with respect to the resources used and their potential environmental impact and to identify critical steps of a chemical synthesis.

We consider as metrics the mass index S^{-1} [Eq. (1)], that is, the mass of all raw materials used for the synthesis including solvents, catalysts, auxiliaries for reaction, and workup per mass unit of the purified product, and the environmental factor E [Eq. (2)], waste per mass unit of the product (waste being all materials used in reaction and workup except the desired product), to characterize quantitatively the reaction input and output, respectively. Evidently, it would be important to also consider energy use and investment, which may differ considering different processes. However, the necessary data are usually not available for lab bench reactions.

$$\text{Mass index } S^{-1} = \Sigma\text{Raw materials [kg]/Product [kg]} \quad (1)$$

$$\text{Environmental factor } E = \Sigma\text{Waste [kg]/Product [kg]} \quad (2)$$

To illustrate the approach we compare three different textbook syntheses and one new literature synthesis of 4-methoxyacetophenone, an example of the very important Friedel–Crafts acylation (Scheme 1).



Scheme 1. Different syntheses of 4-methoxyacetophenone, on the basis of the same substrate using different acylation agents, solvents and catalysts. a) Ref. [29], b) Ref. [30], c) Ref. [31], d) Ref. [32].

Waste treatment—recovery, recycling, deposition etc.—will not be considered in these examples; however, this may be considered as well using EATOS. Clearly, focusing on chemical yields, as most chemists are used to do, reaction d), the classical Friedel-Crafts protocol, would be the best method yielding 93% of the product compared to only 50–60% yields of reactions a)–c). However, very simple calculation of the mass intensities (S^{-1}) and environmental factors (E) of these four reactions by using EATOS reveals clearly the critical areas of the different reaction protocols (Figure 1). At first sight remarkable differences can be observed: mass intensities and environmental factors differ by more than one order of magnitude, with reaction a) having the highest values of about $S^{-1} = 39$ and $E = 38$. That means that 39 kg of materials have to be used and about 38 kg of waste are produced to obtain 1 kg of product. In contrast,

Abstract in German: *Ein einfaches, quantitatives Verfahren wird vorgeschlagen, das dem Chemiker ermöglicht, alternative chemische Synthesen im Hinblick auf ihren Ressourcenbedarf und ihre potentielle Umweltbelastung zu vergleichen. Dieses Verfahren sollte nützlich sein für die systematische Entwicklung nachhaltigerer Prozesse. Wir betrachten als Maßzahl den Massenindex S^{-1} zur Quantifizierung der Ressourceninanspruchnahme und den Umweltfaktor E zur Quantifizierung des Abfalls. Die potentielle Umweltbelastung wird quantifiziert unter Benutzung leicht verfügbarer Daten jeder Verbindung, die bei der Reaktion verwendet wird, und jeder Verbindung, die als Abfall anfällt. Die Rechnungen können leicht durchgeführt werden mit Hilfe des Programms EATOS—Environmental Assessment Tool for Organic Syntheses.*

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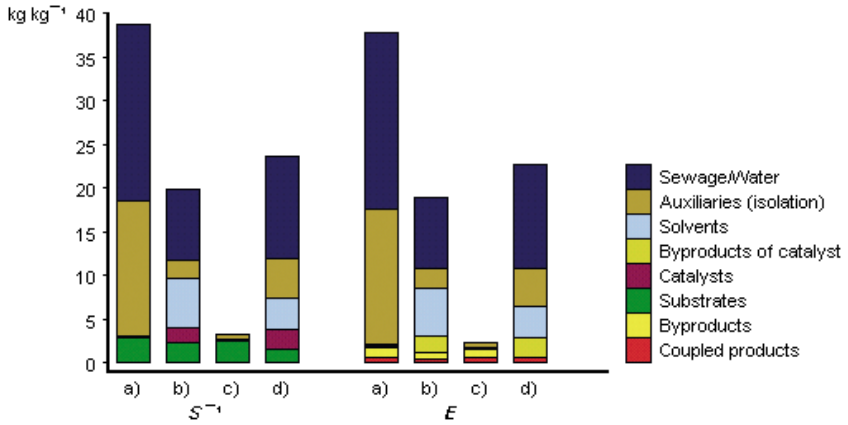

Figure 1. Assessment of the syntheses of 4-methoxyacetophenone (Scheme 1) by means of the software EATOS: mass index S^{-1} and environmental factor E. The detailed data making the differences of the four processes transparent are given in[25] (Tables 1 and 2 in the Supporting Information).

reaction c) shows the lowest mass intensity of $S^{-1} = 3$, that is 2 kg of waste per 1 kg of product. Reactions b) and d) are in between. Evidently, reaction c) yielding only 60% of the product seems to be, with respect to the usage of resources and the waste produced, more advantageous than the other reactions.

Most chemists tend to focus on the chemical reaction to improve the chemical yield. However, to analyze a process with respect to the possibility to reduce the amount of materials used and to minimize the waste it is necessary to study the different elements of the complete process and the technology around the reaction, especially the workup procedure. We consider the quantity of all raw materials used in reaction and workup procedure: substrates, catalysts, reaction auxiliaries, coupled and side products, products possibly formed from the catalyst used, solvents, workup auxiliaries, and sewage. Applying EATOS—based solely on the mass of all chemicals used, the respective stoichiometric equations, and chemical yields—to reactions a)–d) the quantitative differences of mass intensities S^{-1} and environmental factors E of the different processes and the respective contributions of the various categories are visualized (Figure 1,[25]).

The high mass intensity and the high environmental factor of reaction a) is brought about almost exclusively by the workup procedure, which is rather complex, whereas the chemical reaction with iodine as catalyst and no solvent is comparable to reaction c) and less material consuming than reactions b) and d). Thus, the sum of the amount of substrates, catalyst, and solvent used to perform the reaction per kg of product of processes b) and d) are 9.5 kg and 7.2 kg, respectively, in comparison to only 2.8 kg and 2.5 kg of reactions a) and c), respectively. The important advantage of reaction c), which makes use of the same substrates, that is, anisole and acetic anhydride, as reactions a) and d) is the heterogeneous catalyst that can easily be removed by filtration. No material-consuming workup procedure is necessary in contrast to reaction a) that functions by means of a homogeneous catalyst. Furthermore, no solvents and no reagents in stoichiometric amounts are applied; this makes this process advantageous relative to b) and d), which both make use of solvents and aluminum chloride as a reagent in stoichiometric amounts.

To compare alternative synthetic routes solely on the basis of the amount of reactants and waste, although a leading indicator,[15] may be grossly oversimplified. Evidently, the environmental quality of the feed and of the waste is important. For example, it makes a difference if acetic anhydride as in reaction a) or acetyl chloride and aluminum chloride as in reaction b) are used as reactants with anisole, and if the waste consists of relatively innocuous salts such as sodium acetate, chloride, and sulfate in aqueous solution saturated with diethyl ether or of aluminum chloride as an aqueous solution saturated with dichloroethane as in reactions a) and b), respectively.

We have been developing a simple method based on easily available data to estimate such a specific potential environmental impact [PEI kg^{-1}] Q_{min} and Q_{nout} of each compound of the feed and of each compound of the waste, respectively, using EATOS. Compounds having no environmental impact are given a value of $Q_{\mathrm{min}} = Q_{\mathrm{nout}} = 1$ PEI kg^{-1}, increasing with increasing environmental impact up to maxium 10 PEI kg^{-1}.[25, 26] Interestingly, compounds are assessed differently occurring in the feed and in the waste. The impact Q_{min} takes into account the risk measured by the R-phrases of used chemicals[27] and the environmental impact of their production measured by their prices assuming that prices take best into account all the materials and energy being necessary for all steps to synthesize the used chemicals. It is an important aspect of a sustainable development that prices should reflect all environmental and social costs (Agenda 21, Chapter 4). The impact Q_{nout} of the waste compounds takes into account potential ecotoxicological and human toxicological effects.

With Equations (3) and (4), the environmental indices EI_{in} and EI_{out}, the latter corresponding to Sheldons' EQ, of the respective processes can be determined and compared using EATOS (Figure 2).

$$EI_{\mathrm{in}} = Q_{\mathrm{input}} \cdot S^{-1} = \frac{\sum_m Q_{m\,\mathrm{in}}[\mathrm{PEI/kg}] \cdot \mathrm{Raw\ material}_m[\mathrm{kg}]}{\mathrm{Product\ [kg]}} \quad (3)$$

$$EI_{\mathrm{out}} = Q_{\mathrm{output}} \cdot E = \frac{\sum_n Q_{n\,\mathrm{out}}[\mathrm{PEI/kg}] \cdot \mathrm{Waste}_n[\mathrm{kg}]}{\mathrm{Product\ [kg]}} \quad (4)$$

This simple procedure gives an indicator that allows a deepened insight to contrast the different processes with respect to resource usage and potential environmental impact. Dichloroethane that is used as solvent is due to more than 50% of the environmental impact of reaction b). The same applies for reaction a) which makes use of diethyl ether in the workup procedure and reaction d) which makes use of carbon disulfide as reaction solvent and additionally diethyl ether for workup. Evidently, the largest contribution to the environ-

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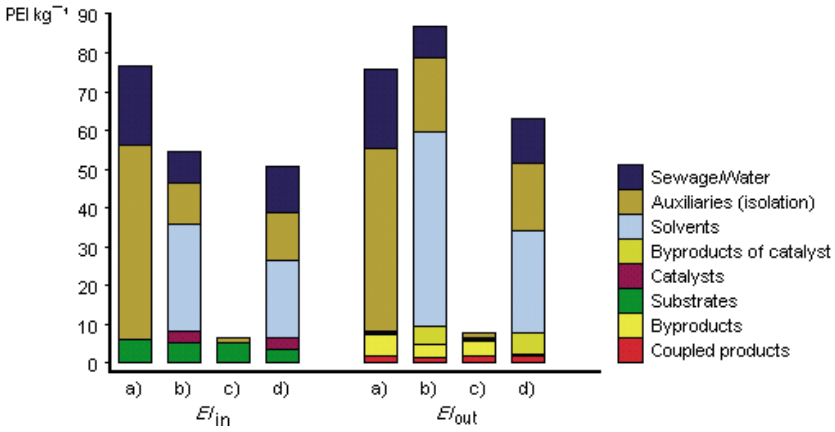

Figure 2. Assessment of the syntheses of 4-methoxyacetophenone (Scheme 1) by means of the software EATOS: environmental indices for input EI_{in} and output EI_{out} (for detailed data see,[25] Tables 3–7 in the Supporting Information), (PEI = potential environmental impact).

mental indices of organic reactions is due to organic solvents in reaction and workup. Thus, it is evident that the reduction of organic solvent use is of great importance for the development of environmentally more benign processes.[28] An example may be reaction c) with environmental indices less than one order of magnitude in comparison to the other reactions mainly because no organic solvents are used in reaction and workup. In principle, these tendencies could already be derived from the discussion of mass intensity and the environmental factor. However, the enormous impact due to the organic solvents becomes most evident considering the environmental indices.

The given examples are very simple one-step reactions. Most often chemists have to consider multistep syntheses and most important is the proper selection of the best way to the desired product. Using EATOS our method can easily be applied also to reaction sequences and allows us to analyze them as discussed for one-step reactions.

Conclusions

We believe we have developed for the first time a reliable methodology for assessing and comparing synthetic organic reactions on a laboratory scale with regard to their resource usage and potential environmental impact. This method can easily be used by all chemists who work in the field of synthesis, both in academia and industry, to analyze their reactions and compare different possible ways to the same target substance to achieve the aim to reduce and eliminate unsustainable patterns. Of course, there exist some important tools in industry to obtain/predict a mass balance and to assess technological consequences in much more detail than EATOS is able to do. However, each detailed analysis has to be performed in specialized units within the company by using high sophisticated tools and of course associated with corresponding costs. Most importantly, the details of the processes have to be known in order to apply these tools and this is only possible relatively late in the development of the respective process. EATOS is a tool to be used on the lab bench in the very beginning to select from a pool of synthetic pathways the most promising alternatives that should be studied and developed in more detail.

We think that the method should be introduced in university courses to enable chemists to learn thinking from the very beginning in the framework of a sustainable development.

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