TECHNOLOGICAL PROCESSES OF ORGANIC SYNTHESIS: PROCESS-LEVEL STRUCTURE, GREEN METRICS AND ENABLING TECHNOLOGIES

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Annotation. This article examines the technological processes of organic synthesis as an integrated system of chemical transformation, separation, purification and waste-management operations rather than as a single reaction step. The aim is to identify, on the basis of published evidence and transparent calculations, the technological decisions that most strongly determine the material efficiency, safety and scalability of organic synthesis. A structured analytical review of peer-reviewed literature (1991–2023) was combined with quantitative evaluation of atom economy for representative reaction types and with a comparative analysis of two industrial case studies: the manufacture of ibuprofen (Boots and BHC routes) and of sitagliptin (rhodium-catalysed asymmetric hydrogenation versus transaminase biocatalysis). The calculations show that atom economy ranges from 100% for addition reactions such as the Diels–Alder reaction and catalytic hydrogenation to 25.7% for the Wittig methylenation of cyclohexanone, and that the change from a stoichiometric six-step route to a catalytic three-step route raises the atom economy of ibuprofen synthesis from about 40% to 77.5%. Published data further indicate that solvents account for the largest share of process mass in fine-chemical and pharmaceutical manufacture, and that continuous-flow, microwave-assisted and biocatalytic technologies improve heat transfer, selectivity or safety under defined conditions. A five-stage decision framework for designing technological processes of organic synthesis is proposed. The results can be used in process development and in teaching organic technology.

Keywords: organic synthesis; chemical technology; process design; atom economy; E factor; green chemistry; continuous-flow chemistry; biocatalysis.

Annotatsiya. Maqolada organik sintezning texnologik jarayonlari yagona kimyoviy o‘zgarish, ajratish, tozalash va chiqindilarni boshqarish operatsiyalaridan iborat tizim sifatida tahlil qilinadi. Tadqiqot maqsadi – nashr etilgan ma’lumotlar va shaffof hisob-kitoblar asosida organik sintezning material samaradorligi, xavfsizligi va masshtablanuvchanligini belgilovchi texnologik qarorlarni aniqlashdir. Ilmiy adabiyotlarning tizimli tahlili (1991–2023), vakillik reaksiya turlari uchun atom iqtisodini hisoblash hamda ikkita sanoat misoli – ibuprofen (Boots va BHC usullari) va sitagliptin (rodiy katalizatorli asimmetrik gidrogenlash va transaminaza biokatalizi) sintezini qiyosiy tahlil qilish uyg‘unlashtirildi. Hisob-kitoblarga ko‘ra, atom iqtisodi Dils–Alder reaksiyasi va katalitik gidrogenlashda 100 %, sikloheksanonning Vittig metilenlanishida esa 25,7 % ni tashkil etadi; olti bosqichli stexiometrik usuldan uch bosqichli katalitik usulga o‘tish ibuprofen sintezida atom iqtisodini taxminan 40 % dan 77,5 % gacha oshiradi. Uzluksiz oqimli, mikroto‘lqinli va biokatalitik texnologiyalar muayyan sharoitlarda issiqlik almashinuvi, selektivlik yoki xavfsizlikni yaxshilashi ko‘rsatilgan. Organik sintez texnologik jarayonlarini loyihalash uchun besh bosqichli qaror qabul qilish sxemasi taklif etiladi.

Kalit so‘zlar: organik sintez; kimyoviy texnologiya; jarayonni loyihalash; atom iqtisodi; E-faktor; yashil kimyo; uzluksiz oqimli kimyo; biokataliz.

Аннотация. В статье технологические процессы органического синтеза рассматриваются как единая система операций химического превращения, разделения, очистки и обращения с

отходами. Цель работы – на основе опубликованных данных и прозрачных расчётов выявить технологические решения, в наибольшей степени определяющие материальную эффективность, безопасность и масштабируемость органического синтеза. Структурированный анализ рецензируемой литературы (1991–2023 гг.) сочетался с расчётом атомной экономии типовых реакций и сравнением двух промышленных примеров: синтеза ибупрофена (методы Boots и BHC) и ситаглиптина (асимметрическое гидрирование на родиевом катализаторе и биокатализ трансаминазой). Расчёты показали, что атомная экономия составляет 100 % для реакции Дильса–Альдера и каталитического гидрирования и 25,7 % для метиленирования циклогексанона по Виттигу; переход от шестистадийного стехиометрического к трёхстадийному каталитическому процессу повышает атомную экономию синтеза ибупрофена примерно с 40 до 77,5 %. Показано, что непрерывно-поточные, микроволновые и биокаталитические технологии в определённых условиях улучшают теплообмен, селективность или безопасность. Предложена пятиэтапная схема принятия решений при проектировании технологических процессов органического синтеза.

Ключевые слова: органический синтез; химическая технология; проектирование процессов; атомная экономия; Е-фактор; зелёная химия; проточная химия; биокатализ.

1. INTRODUCTION

Organic synthesis is the methodological basis for the manufacture of pharmaceuticals, agrochemicals, polymers, dyes, flavours and fragrances, and functional materials. In a research laboratory a synthesis is usually judged by whether the target compound is obtained in acceptable yield and purity. In industrial practice, and increasingly in dissertation research that aims at practical application, this criterion is insufficient: a technological process of organic synthesis comprises not only the chemical transformation itself but also the preparation of raw materials, the control of heat and mass transfer, the isolation and purification of the product, the recovery of solvents and the treatment of waste streams (Stoessel, 2008; Sheldon, 2017).

The material consequences of this broader view are considerable. Sheldon (2007, 2017) defined the environmental factor (E factor) as the mass of waste generated per unit mass of product and showed that it rises from below 0.1 kg/kg in oil refining to between 5 and more than 50 kg/kg in fine chemicals and between 25 and more than 100 kg/kg in the pharmaceutical industry. The main reasons are the multistep character of the syntheses, the use of stoichiometric rather than catalytic reagents, and the large volumes of solvents. These figures show that the technological design of a synthesis, and not only its chemistry, determines how much material is consumed and discarded.

Two conceptual advances have shaped the response of the chemical community. Trost (1991) proposed atom economy as a measure of the fraction of reactant mass that is incorporated into the desired product, and Anastas and Warner (1998) formulated twelve principles of green chemistry that connect molecular design with process design. Since then, mass-based metrics, solvent-selection guides, continuous-flow reactors, microwave heating and engineered enzymes have become part of the toolkit of process chemists (Dunn, 2012; Plutschack et al., 2017; Sheldon & Woodley, 2018).

These developments, however, are usually reported in separate, specialised publications. For researchers preparing dissertations on organic synthesis there is a need for a compact, quantitatively grounded account that shows how individual decisions – route selection, solvent choice, catalyst type, reactor type and safety assessment – combine into one technological process. The present article addresses this need.

The aim of the study is to identify, on the basis of published evidence and transparent calculations, the technological decisions that most strongly influence the material efficiency, safety and

scalability of organic synthesis, and to propose a decision framework for designing such processes. To achieve this aim the following **objectives** were set:

1. to describe the technological structure of an organic synthesis as a sequence of unit operations and decision points;
2. to calculate and compare the atom economy of representative reaction types;
3. to analyse two industrial case studies, ibuprofen and sitagliptin, in which a change of technology produced documented improvements;
4. to compare batch, continuous-flow, microwave-assisted and biocatalytic technologies by their documented advantages and limitations;
5. to formulate a framework for the design of technological processes of organic synthesis.

The novelty of the work lies in combining independently recalculated metrics, case-based evidence and a technology comparison in one process-level framework intended for use in dissertation research and teaching.

2. LITERATURE REVIEW

2.1. Metrics for assessing the efficiency of synthetic processes

Trost (1991) argued that synthetic efficiency should be judged not only by chemical yield but also by the extent to which the atoms of the reactants are incorporated into the product, a criterion he called atom economy. Sheldon (2007) complemented it with the E factor, which is obtained from the mass balance of a real process and therefore captures the contribution of solvents, auxiliary reagents and work-up materials that atom economy ignores. In the pharmaceutical industry the closely related process mass intensity (PMI), the total mass of materials used per unit mass of product, has been adopted as a benchmarking metric because it is simple to calculate and easy to communicate (Jiménez-González et al., 2011). Constable et al. (2002) compared several mass-based metrics used in industry and discussed their relative usefulness, while Roschangar et al. (2015) introduced the Green Aspiration Level, which takes the complexity of a synthesis into account when setting waste-reduction targets. A consistent message of this literature is that no single metric is sufficient and that atom economy, E factor or PMI, and hazard-based assessment should be used together.

2.2. Solvents and auxiliary materials

Solvents are among the largest contributors to process mass in batch syntheses and a main source of safety and environmental concern. Capello et al. (2007) developed a framework for the environmental assessment of solvents that combines environmental, health and safety hazards with the life-cycle energy demand of production and disposal. The CHEM21 consortium proposed a selection guide that classifies classical and less classical solvents as recommended, problematic or hazardous on the basis of safety, health and environmental criteria (Prat et al., 2016); in this guide water, ethanol and ethyl acetate are ranked favourably, whereas dichloromethane and dipolar aprotic amide solvents such as *N,N*-dimethylformamide and *N*-methyl-2-pyrrolidone are not.

2.3. Catalysis and biocatalysis

Catalytic transformations reduce the need for stoichiometric reagents and the corresponding inorganic salts. Sheldon et al. (2007) reviewed homogeneous, heterogeneous and biocatalytic systems from this perspective. Sheldon and Woodley (2018) summarised the role of biocatalysis in sustainable chemistry, noting that enzymes operate under mild conditions, usually in aqueous media, and that protein engineering and directed evolution allow enzymes to be adapted to non-natural substrates and process conditions. The manufacture of the antidiabetic drug sitagliptin with an engineered transaminase is one of the best-documented examples (Savile et al., 2010).

2.4. Continuous-flow and microwave technologies

In flow chemistry, reactions are carried out in narrow channels or tubes through which the reagents are pumped continuously. The small channel dimensions give a high surface-to-volume ratio and therefore efficient heat and mass transfer, while the small volume of reacting material at any moment reduces the inventory of hazardous intermediates (Gutmann et al., 2015; Plutschack et al., 2017). Hessel et al. (2013) described "novel process windows", that is, operating regimes of high temperature, pressure or concentration that become accessible in flow reactors. Microwave heating, reviewed by Kappe (2004), transfers energy directly to polar molecules and allows rapid heating and, in sealed vessels, superheating of solvents above their atmospheric boiling points; the same review concludes that most reported rate accelerations can be rationalised by thermal effects, while the existence of specific non-thermal microwave effects remains debated.

2.5. Process safety and quality assurance

Thermal risk assessment is a prerequisite for scaling up exothermic reactions. Stoessel (2008) presents a systematic approach in which the reaction enthalpy, the adiabatic temperature rise and the consequences of a cooling failure are evaluated and scenarios are classified by criticality. In pharmaceutical manufacture, the ICH Q8(R2) guideline (ICH, 2009) introduced the concepts of quality by design and design space, and the framework on process analytical technology (PAT) published by the U.S. Food and Drug Administration (FDA, 2004) encouraged real-time measurement of critical quality attributes.

2.6. Research gap

The literature thus offers well-developed individual tools, but few compact treatments that integrate them at the level of the whole technological process. In particular, atom-economy calculations, mass-based metrics, solvent guides and reactor-technology reviews are rarely brought together with worked numerical examples. This gap motivates the analytical approach adopted below.

3. RESEARCH METHODOLOGY

3.1. Study design

The study is an analytical, secondary-data investigation. It combines (i) a structured narrative review of the literature, (ii) independent calculation of green-chemistry metrics from balanced reaction equations, and (iii) a comparative analysis of two industrial case studies. No new laboratory experiments were performed; all experimental data are taken from the cited publications, and all calculated values were obtained by the author.

3.2. Selection of sources

Sources were selected from major scientific databases and publisher platforms (Scopus, Web of Science, ScienceDirect, and the platforms of the American Chemical Society, the Royal Society of Chemistry and Wiley) using combinations of the terms "organic synthesis", "process chemistry", "atom economy", "E factor", "process mass intensity", "continuous flow", "microwave-assisted synthesis" and "biocatalysis". The review covers the period from 1991, the year of Trost's paper on atom economy, to 2023. Peer-reviewed articles, review papers, standard monographs and regulatory guidelines were included; unreviewed commercial materials and patents without independent validation were excluded. Case studies were chosen according to three criteria: industrial relevance, availability of quantitative data in peer-reviewed or authoritative sources, and the existence of a documented comparison between an older and a newer technology.

3.3. Calculation of metrics

Atom economy (AE) was calculated from the balanced equation of each reaction as

$$\mathrm{AE}\ (\%) = [M_r(\text{desired product}) / \Sigma M_r(\text{all reactants})] \times 100, \quad (1)$$

where M_r is the molar mass. Molar masses were computed from standard atomic masses (C 12.011; H 1.008; O 15.999; P 30.974) and are given to two decimal places. The E factor and process mass intensity are defined as

$$E = m_{waste} / m_{product}; \quad PMI = m_{input} / m_{product}; \quad E = PMI - 1, \quad (2)$$

where m denotes mass and the relationship $E = PMI - 1$ holds when the same system boundaries (for example, the treatment of water) are applied to both metrics. For the case studies, process-level values were taken from the cited sources and were not re-estimated.

3.4. Limitations of the approach

Atom economy is a theoretical quantity that assumes full conversion and stoichiometric amounts; it excludes solvents, excess reagents and work-up materials. Published E-factor values depend on the system boundaries chosen by the authors, and case-study data originate from specific manufacturers and may not transfer to other processes. The conclusions should therefore be read as evidence-based guidance for design, not as universal rules.

4. ANALYSIS AND MAIN RESULTS

1. Technological structure of an organic synthesis

An organic synthesis can be represented as a sequence of seven groups of operations (Table 1). Each group involves its own decision variables and contributes differently to material consumption, energy demand and risk.

Table 1. Unit operations and decision points in a technological process of organic synthesis

Stage	Typical operations	Main decision variables	Main consequence
1. Preparation of raw materials	Quality control of reagents, drying of solvents, charging	Purity, supplier, hazard of materials	Impurity profile of the product
2. Chemical transformation	Reaction in a batch, flow or microwave reactor; dosing; temperature and pressure control	Kinetics, heat release, selectivity, catalyst	Yield, selectivity, thermal safety
3. Work-up and isolation	Quenching, extraction, phase separation, filtration	Solvent and water volumes, reagent removal	Solvent and aqueous waste
4. Purification	Crystallisation, distillation, chromatography	Required purity, physical properties of the product	Yield loss, solvent consumption
5. Drying and finishing	Vacuum drying, milling, packaging	Thermal stability, physical form	Product stability, energy demand
6. Waste and solvent management	Solvent recovery, neutralisation, treatment of by-products	Recovery efficiency, regulation	E factor, disposal cost

Stage	Typical operations	Main decision variables	Main consequence
7. Analytical control	In-process analysis (HPLC, IR, NMR, calorimetry)	Critical quality attributes, sampling frequency	Process robustness, reproducibility

Source: compiled by the author on the basis of Stoessel (2008), Sheldon (2017) and ICH (2009).

Two observations follow. First, the chemical transformation (stage 2) is only one of seven decision points; solvents, water and auxiliary materials are mainly consumed in stages 3, 4 and 6, which are often not considered at the stage of reaction development. Second, the stages are coupled: the choice of reaction solvent determines the work-up, the work-up determines the purification method, and the purification method determines the waste stream. A technological process must therefore be designed and optimised as a whole. One practical consequence is "telescoping", the performance of consecutive steps without isolating intermediates, which removes entire isolation and purification stages.

4.2. Atom economy of representative reactions

Table 2 presents atom economy calculated by Eq. (1) for five reaction types commonly used in organic synthesis.

Table 2. Atom economy of representative organic reactions (author's calculations)

Reaction type	Example	Calculation, M_r (g/mol)	AE, %
Cycloaddition	Diels–Alder reaction of 1,3-butadiene with ethylene giving cyclohexene	All reactant atoms are retained in the product	100
Catalytic hydrogenation	Alkene + H_2 → alkane	All reactant atoms are retained in the product	100
Esterification	$CH_3COOH + C_2H_5OH \rightarrow CH_3COOC_2H_5 + H_2O$	88.11 / (60.05 + 46.07) = 88.11 / 106.12	83.0
Friedel–Crafts acylation	Isobutylbenzene + acetic anhydride → 4-isobutylacetophenone + CH_3COOH	176.26 / (134.22 + 102.09) = 176.26 / 236.31	74.6
Wittig methylenation	Cyclohexanone + $Ph_3P{=}CH_2$ → methylenecyclohexane + $Ph_3P{=}O$	96.17 / (98.15 + 276.32) = 96.17 / 374.46	25.7

Note: AE is a theoretical value for 100% conversion and stoichiometric quantities.

The calculated values show that atom economy is determined primarily by reaction type. Addition reactions, such as Diels–Alder cycloaddition and catalytic hydrogenation, incorporate all reactant atoms in the product and have an atom economy of 100%. Condensation reactions that release

a small molecule, such as esterification (83.0%) and Friedel–Crafts acylation with an acid anhydride (74.6%), have intermediate values because water or a carboxylic acid is formed as co-product. Reactions that generate a high-molar-mass co-product have the lowest values: in the Wittig methylenation of cyclohexanone, triphenylphosphine oxide (M = 278.29 g/mol) accounts for about three quarters of the total mass of products, and the atom economy falls to 25.7%.

It should be emphasised that a favourable atom economy does not guarantee a low waste output. Atom economy ignores solvents, excess reagents and work-up materials, which is why the E factor and PMI of the complete process have to be determined from the mass balance. The published E factors summarised in Table 3 illustrate the scale of this effect.

Table 3. E factors in different sectors of the chemical industry

Industry sector	Annual product tonnage	E factor, kg waste per kg product
Oil refining	10^6–10^8	< 0.1
Bulk chemicals	10^4–10^6	< 1 to 5
Fine chemicals	10^2–10^4	5 to > 50
Pharmaceuticals	10–10^3	25 to > 100

Source: Sheldon (2017).

The E factor increases by about three orders of magnitude as production volume decreases and molecular complexity increases (Table 3). Fine-chemical and pharmaceutical products require longer synthetic sequences, in which each step adds solvents, reagents and work-up materials. This confirms that step economy – the number of steps needed to reach the target – is as important as the efficiency of any single step.

4.3. Case study 1: technological redesign of ibuprofen synthesis

The synthesis of the analgesic ibuprofen is a classical example of the effect of technological redesign. The original process of the Boots Company consisted of six steps starting from isobutylbenzene: Friedel–Crafts acylation with acetic anhydride in the presence of stoichiometric aluminium chloride, Darzens condensation with ethyl chloroacetate, hydrolysis and decarboxylation to an aldehyde, conversion to an oxime with hydroxylamine, dehydration to a nitrile, and hydrolysis to the carboxylic acid. The later BHC process uses three steps: acylation of isobutylbenzene with acetic anhydride in anhydrous hydrogen fluoride, catalytic hydrogenation of the ketone over Raney nickel, and palladium-catalysed carbonylation of the resulting alcohol (Cann & Connelly, 2000). The BHC process received the U.S. Presidential Green Chemistry Challenge Award in 1997.

Table 4. Comparison of the Boots and BHC routes to ibuprofen

Parameter	Boots route	BHC route
Number of synthetic steps	6	3

Parameter	Boots route	BHC route
Overall atom economy	≈ 40% (literature value)	77.5% (calculated); ≈ 99% if acetic acid is recovered and reused (literature value)
Acylation system	Acetic anhydride with stoichiometric $AlCl_3$	Acetic anhydride with anhydrous HF (catalyst and solvent, recovered and reused)
Subsequent key steps	Darzens condensation, decarboxylation, oximation, dehydration, hydrolysis	Catalytic hydrogenation (Raney nickel); Pd-catalysed carbonylation
Principal waste	Large amounts of aluminium-containing and other inorganic salts	Acetic acid (co-product that can be recovered)

Sources: Cann and Connelly (2000); atom economy of the BHC route calculated by the author.

The author's calculation confirms the literature value for the BHC route. The total mass of reactants for the sequence (isobutylbenzene 134.22 + acetic anhydride 102.09 + H_2 2.02 + CO 28.01 = 266.34 g/mol) gives an atom economy of 206.29 / 266.34 = 77.5% for ibuprofen (M = 206.29 g/mol). The hydrogenation and carbonylation steps are both addition reactions with 100% atom economy; the whole loss of 22.5% of reactant mass is due to the single co-product, acetic acid (60.05 g/mol), formed in the acylation step. Because acetic acid is a useful commodity chemical, its recovery raises the effective atom economy towards the ≈ 99% reported in the literature. The analysis shows that the improvement results from three technological decisions: reducing the number of steps, replacing a stoichiometric Lewis acid with a recoverable catalyst, and using addition-type catalytic steps.

The case also illustrates that green metrics must be interpreted together with hazard assessment. Anhydrous hydrogen fluoride is highly toxic and corrosive, and its use is acceptable only in closed systems with efficient recovery. The improved metrics of the BHC process therefore depend on engineering controls, and a complete evaluation must include safety as an independent criterion.

4.4. Solvent selection and recovery

Because solvents dominate the process mass of many batch syntheses (Jiménez-González et al., 2011; Sheldon, 2017), solvent decisions have a disproportionate effect on the E factor. Three measures follow from the literature reviewed. First, solvents should be selected using a structured guide: the CHEM21 guide (Prat et al., 2016) and the framework of Capello et al. (2007) allow solvents to be ranked consistently, and replacing hazardous solvents such as dichloromethane, *N,N*-dimethylformamide and *N*-methyl-2-pyrrolidone by recommended ones (for example ethanol, 2-propanol, ethyl acetate or water) should be considered at the earliest stage of route design. Second, the volume of solvent should be minimised by operating at higher concentrations and by telescoping steps. Third, the unavoidable solvent should be recovered, typically by distillation, and reused, with the recovery efficiency included in the mass balance. These measures act on stages 3, 4 and 6 of Table 1, where most solvent consumption occurs.

4.5. Case study 2: biocatalytic manufacture of sitagliptin

Sitagliptin, a drug for type 2 diabetes, contains a chiral primary amine. In the first-generation manufacturing process the stereogenic centre was created by asymmetric hydrogenation of an enamine intermediate using a rhodium catalyst with a chiral ferrocenyl diphosphine ligand under high hydrogen pressure; the product then required treatment to remove rhodium and to raise enantiomeric purity (Savile et al., 2010). In the second-generation process, an (*R*)-selective transaminase converts the corresponding prochiral ketone directly to the amine, using isopropylamine as the amino donor. The wild-type enzyme was inactive towards the bulky substrate, and an efficient biocatalyst was obtained by directed evolution combined with substrate-walking and computational design (Savile et al., 2010).

Savile et al. (2010) reported that the biocatalytic route gave the product with an enantiomeric excess above 99.95%, a 10–13% increase in overall yield, a 53% increase in productivity (kilograms per litre per day) and a 19% reduction in total waste, and that it eliminated the use of transition-metal catalyst and the need for specialised high-pressure hydrogenation equipment. The case shows that enzyme engineering can make a biocatalytic step competitive for an industrial substrate, and that the benefits are realised at several stages of Table 1 simultaneously: reaction selectivity (stage 2), removal of metal residues (stage 4) and the type of equipment required. The principal limitation is the development effort: the enzyme had to be evolved over many rounds, so biocatalysis is most attractive when the product volume or value justifies this investment

4.6. Enabling reactor technologies

Heat transfer is a fundamental constraint in scaling up exothermic reactions. For geometrically similar vessels, the heat released by a reaction is proportional to the reaction volume (proportional to L^3, where L is a characteristic length), whereas the heat that can be removed through the walls is proportional to the surface area (L^2). The surface-to-volume ratio, which scales as $1/L$, therefore falls tenfold when the linear dimension is increased tenfold, and heat removal becomes progressively more difficult on scale-up. Flow reactors counteract this by keeping at least one dimension very small, which is why they are favoured for fast, strongly exothermic or hazardous reactions (Gutmann et al., 2015; Plutschack et al., 2017). Table 5 summarises the documented advantages and limitations of four technologies.

Table 5. Comparison of technologies for the reaction stage of organic synthesis

Technology	Principal technological advantages	Principal limitations	Key sources
Batch stirred-tank reactor	Flexible multipurpose equipment; well-established practice; suitable for slow reactions and solids	Heat removal decreases on scale-up; large inventory of hazardous material	Stoessel (2008)
Continuous-flow reactor	High surface-to-volume ratio; efficient heat and mass transfer; small hazardous inventory; access to extended temperature and pressure ranges	Risk of clogging by solids; dedicated equipment; less suited to very slow reactions	Hessel et al. (2013); Gutmann et al. (2015); Plutschack et al. (2017)

Technology	Principal technological advantages	Principal limitations	Key sources
Microwave-assisted reactor	Rapid volumetric heating; superheating of solvents in sealed vessels; short reaction times	Limited penetration depth and scale-up; non-thermal effects debated	Kappe (2004)
Biocatalytic process	High chemo-, regio- and enantioselectivity; mild, usually aqueous conditions	Enzyme stability and substrate scope; development effort for enzyme engineering	Sheldon & Woodley (2018); Savile et al. (2010)

Source: compiled by the author from the cited literature.

No technology is universally superior. The choice depends on reaction kinetics, heat release, the presence of solids, hazard of intermediates, required selectivity and production volume. For this reason the decision should be taken after quantitative screening (Section 4.8), not by default.

4.7. Process safety and quality control

Process safety must be assessed before the scale of a reaction is increased. A basic quantity is the adiabatic temperature rise, which estimates the temperature increase if all the reaction heat were retained in the mixture:

$$\Delta T_{ad} = (-\Delta H_r \cdot n) / (m \cdot c_p), \quad (3)$$

where ΔH_r is the reaction enthalpy per mole, n is the amount of substance reacted, m is the mass of the reaction mixture and c_p is its specific heat capacity. As an illustrative calculation, for a reaction with $\Delta H_r = -100$ kJ/mol (a magnitude typical of many exothermic organic reactions), a concentration of 1 mol per kg of mixture and $c_p = 2$ kJ/(kg·K), $\Delta T_{ad} = 100 \times 1 / (1 \times 2) = 50$ K. If cooling fails, the mixture could therefore heat by 50 K, which may be enough to reach a temperature at which secondary decomposition begins. Stoessel (2008) proposes to combine such values with the maximum temperature that could be reached on loss of cooling and the temperature at which a decomposition reaction would take 24 hours to reach maximum rate, in order to classify the criticality of a process.

For quality control, ICH Q8(R2) recommends defining a design space within which process parameters can be varied without affecting product quality (ICH, 2009), and the PAT framework of the FDA (2004) supports real-time in-line or on-line measurement of critical attributes. In terms of Table 1, these tools link stage 7 to stages 2–5 and make the process robust and reproducible.

4.8. Proposed framework for designing technological processes of organic synthesis

The evidence reviewed above can be organised as a five-stage framework that can be applied in dissertation research and in process development:

1. **Route selection and step economy.** Compare alternative routes by the number of steps and by the atom economy of each step (Eq. 1); prefer addition-type and catalytic steps and avoid high-molar-mass co-products.
2. **Quantitative screening.** Estimate PMI or E factor for the leading routes from laboratory mass balances, including solvents and work-up materials; rank solvents using a structured guide.

3. **Technology selection.** Select the reactor and catalytic technology (batch, flow, microwave, biocatalysis; Table 5) on the basis of kinetics, heat release, solids handling and required selectivity.
4. **Safety and quality assessment.** Determine reaction enthalpy and adiabatic temperature rise (Eq. 3), evaluate decomposition hazards, and define critical quality attributes and in-process controls.
5. **Waste and solvent management.** Plan solvent recovery, treatment of co-products and, where possible, valorisation of by-products (as in the case of acetic acid in the BHC process); then repeat the screening with the improved mass balance.

The framework is iterative: results at any stage may require a return to route selection.

4.9. Discussion

The results agree with the general picture drawn by Sheldon (2007, 2017) and Trost (1991): material efficiency is governed primarily by route design and by the choice between stoichiometric and catalytic reagents. The ibuprofen case adds a quantitative detail that is not always stated explicitly – the whole atom-economy loss of the BHC route can be traced to a single recoverable co-product – while the sitagliptin case demonstrates that the benefits of a technology change also appear outside the reaction step, in purification and equipment requirements. The comparison of technologies indicates that flow chemistry, microwave heating and biocatalysis address different constraints and are therefore complementary. The main limitations of the study are its reliance on published data and the absence of original experimental verification; the proposed framework should be tested on specific syntheses with measured mass balances.

5. CONCLUSION AND RECOMMENDATIONS

The analysis leads to the following conclusions:

1. A technological process of organic synthesis is a system of at least seven coupled groups of operations; the reaction step alone does not determine the material efficiency, safety or cost of the process.
2. Atom economy depends mainly on reaction type: it is 100% for addition reactions (Diels–Alder cycloaddition, catalytic hydrogenation), 83.0% for esterification, 74.6% for Friedel–Crafts acylation with an anhydride and 25.7% for Wittig methylenation of cyclohexanone. Because it ignores solvents and auxiliary materials, it must be supplemented by E factor or PMI.
3. Reported E factors rise from below 0.1 in oil refining to between 25 and more than 100 in the pharmaceutical industry, which reflects multistep syntheses, stoichiometric reagents and solvent use.
4. In the ibuprofen case, the change from the six-step Boots route to the three-step BHC route raises the atom economy from about 40% to 77.5%, and the remaining loss is caused solely by acetic acid, which can be recovered. In the sitagliptin case, replacing metal-catalysed hydrogenation by an engineered transaminase improved yield, productivity and waste reduction and eliminated the transition-metal catalyst.
5. Continuous-flow, microwave-assisted and biocatalytic technologies address different technological constraints; their choice must be based on quantitative screening and safety assessment, and a five-stage framework for such decisions is proposed.

Recommendations. (1) Researchers developing new syntheses should report atom economy for each step and, wherever laboratory mass balances are available, E factor or PMI of the whole procedure including solvents and work-up materials. (2) Solvents should be selected with a structured guide at the earliest stage of route design, and solvent recovery should be included in the mass balance. (3) A thermal hazard assessment, including the adiabatic temperature rise, should precede any increase in reaction scale. (4) Courses in organic technology can use the worked calculations and the case

studies presented here as teaching material. (5) Further research should test the proposed framework on specific syntheses, comparing batch and continuous-flow implementations by measured PMI, productivity and safety indicators.

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