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Continuous-Flow Chemistry in Chemical Education

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While continuous-flow chemistry is steadily increasing its footprint in academic research and in the manufacturing of pharmaceutical intermediates and fine chemicals, the attention for flow chemistry in educational programs is on average rather limited. This account is meant to provide a personal overview of the possibilities to address the involvement of flow chemistry in the various stages of chemical education.

Keywords: Continuous-flow chemistry, chemistry education, teaching modules, sustainable chemistry

Introduction

Continuous processing has a long history in the production of chemicals at bulk scale. In fact, the majority of bulk chemicals is being produced in a continuous manufacturing process. However, batchwise production has traditionally been the process of choice for the production of fine chemicals and pharmaceuticals, which takes place at a scale of hundreds to thousands of kilograms. On the one hand, this situation logically follows from the fact that at laboratory scale, both in academic and industrial labs, all chemical reactions are typically carried out in batch, including optimization at larger scale. On the other hand, also the financial aspect is important: multipurpose (pilot) plants can continuously be used for virtually any chemical reaction and are therefore cost efficient to operate. Nevertheless, since two decades or so, continuous-flow chemistry has become more widespread in academic synthetic chemistry groups that recognized the benefits of conducting chemical reactions in a continuous manner in small-volume microreactors [1]. The intrinsic safety, the relatively good mass and heat transport, the excellent control over reaction conditions and hence the reproducibility of reactions, have spurred a steadily growing number of chemists to use continuous-flow reactions as the mode of operation [2]. In addition, process chemists in the fine chemical and pharmaceutical industry have been increasingly keen on applying continuous-flow reactions for new processes [3]. Considering the advantages of flow chemistry, and its increasing relevance for pharmaceutical and fine chemical production, it is important that also more attention is devoted to continuous-flow chemistry in chemistry education. This is not yet the case; the education of our students still largely proceeds through traditional chemistry laboratory courses, compiled of batchwise experiments. In this overview, we will highlight opportunities to improve the chemical education of chemistry students in various stages of their careers. This review is focused on the chemistry curricula in higher education at regular universities, not in chemical engineering programs at technical universities, where teaching about continuous processes, transport phenomena, etc. is an integral part of the educational programs.

Bachelor's Programs

The bachelor's program is obviously the most basic part of higher education in chemistry. At this stage of the study program, there is typically no clear link with research yet and knowledge transfer is mainly focused on teaching the fundamental aspects of chemistry and chemical reactions. Experimental training usually proceeds in a conventional way, making use of regular textbooks for laboratory courses. This part of the chemical education has not changed much over the past decades, while ideally it should also follow the important trends in experimental chemistry research. This period is the time when students start doing their first laboratory experiments, and it would didactically be very important to introduce flow chemistry elements in this phase rather than performing all practical training in conventional batchwise reactions. However, this practice requires, among others, some fundamental knowledge of flow chemistry, the availability of educational modules, and suitable flow equipment that can be used in a chemistry laboratory course. Crucially, it moreover requires visionary thinking of teaching staff who are willing to invest time and to make financial efforts to incorporate flow chemistry principles in elementary laboratory courses. Nevertheless, we think that it is essential that especially in this early stage students realize that experiments can be performed either in batch or in flow and early on consider continuous flow as a viable alternative for batch reactions. Concerning the implementation of flow chemistry experiments in teaching modules, there is more material becoming (commercially) available that can be readily used for education. Some possibilities include the following:

- The general availability of detailed experimental procedures that are optimized for application in educational modules. An early example by Wirth et al. [4a] provides general background information on flow chemistry and detailed procedures that can be readily adapted for application in an undergraduate laboratory course, but there are also other examples [4b]. Somewhat more advanced cases involve highly detailed procedures by Noël [5], and also recently by Kappe [6], describing how a continuous-flow setup can be constructed from commercially available parts (pumps, tubes, and connectors instead of flasks, reflux condensors, and other glassware) and how experiments can be safely conducted in this setup. It would didactically be advantageous to include the construction of the flow setup in the laboratory course (as students traditionally do with flasks, reflux condensors, Schlenk conditions, etc.) since these publications show that flow experiments can be carried out without the requirement of (expensive) more advanced and/or automated flow equipment from commercial suppliers.
- Education packages provided by commercial suppliers. Nowadays, a number of commercial suppliers of continuous-flow equipment are also providing teaching modules sometimes linked to the use of their own equipment. An early provider was the company FutureChemistry [7], offering fully fledged educational continuous flow modules, while several other companies followed and currently also provide rather elaborate teaching manuals [8].

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Master's Programs

These programs typically have a much stronger link between education and research than the Bachelor's programs. Besides the fact that lectures contain more advanced chemistry topics and deal with current trends in research, in many countries, a major part of the Master's education consists of scientific training (internship) in a research group. Hence, students might be able to choose research topics that involve continuous-flow chemistry and thus gain experience in this field. In the early years of flow chemistry, continuous-flow experiments were largely restricted to focusing on improving or more safely conducting reactions that were traditionally carried out in batch. In recent years, there has been a shift in focus towards topics where flow chemistry has clear advantages over batch chemistry. Particular areas include photochemistry [9] and photoredox chemistry [10], both traditionally being limited in application since reactions involving the use of light are poorly scalable in batch. The advent of flow chemistry, however, has significantly contributed to the wider application of photochemistry and photoredox chemistry, since the flow process makes the photochemical process readily scalable. The enormous growth in the number of groups that are currently involved in photoredox chemistry in flow also causes that a much larger percentage of master students do gain experience with flow chemical reactions. Other areas where flow chemistry offers particular advantages over batch chemistry include the use of enzymatic reactions [11], ultrashort (flash) reactions [12], and extended process windows (high temperature, high pressure) [13], and all of these rapidly developing areas would offer interesting opportunities for master's students.

PhD Programs

Similar arguments hold in fact for education in flow chemistry at the PhD level. In addition, we strongly feel that PhD students should be stimulated much more to start implementing flow chemistry experiments in their own research project. This concept was successfully implemented in the Initial Training Network ECHONET [14], where all early stage researchers received training on flow chemistry during a Summer School, where part of the program consisted of students drawing up a research plan to implement flow chemistry elements in their own research project. In a number of cases, this was also experimentally implemented and led to the students appreciating the advantages of flow chemistry and also to new scientific publications. In fact, more generally researchers should realize that whenever they have to repeatedly carry out the same reaction (either to optimize, determine the scope, or determine the kinetics of the reaction), it is advantageous to conduct the reaction in flow, due to the superior control over the reaction conditions and hence reproducibility of the process.

Nowadays, a growing number of commercially available books provide ample background, information, and experimental procedures on continuous-flow reactions to further stimulate PhD students to embark on continuous-flow chemistry [15]. In addition, more and more flow chemistry reactions are introduced to the audience on conferences, workshops, and progress meetings in synthetic organic chemistry. PhD students must be continuously stimulated to think of new possibilities of flow chemistry and implement this into their own projects.

In summary, over the past two decades, continuous-flow chemical reactions have risen from the level of peculiarity to a full-fledged field in organic synthesis with importance for the manufacturing of fine chemicals and pharmaceuticals. The most recent years have shown an enormous growth of the use of flow chemistry in fields where traditional batch chemistry is limited in terms of scale up and safety. This trend will continue, and we are confident that this new way of conducting chemical reactions will lead in future research to – at this moment unforeseen – opportunities in the years to come. This also puts a moral duty on the more senior chemists to stimulate as much as possible the use of continuous-flow chemistry at every stage of chemical education.

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References

1. Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796–11893.

2. (a) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728; (b) Gemoets, H. P. L.; Su, Y.; Shang, M.; Hessel, V.; Luque, R.; Noel, T. *Chem. Soc. Rev.* **2016**, *45*, 83–117; (c) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.

3. Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process. Res. Dev.* **2016**, *20*, 2–25.

4. (a) König, B.; Kreitmeier, P.; Hilgers, P.; Wirth, T. *J. Chem. Educ.* **2013**, *90*, 934–936; (b) Feng, Z. V. Edelman, K. R.; Swanson, B. P. *J. Chem. Educ.* **2015**, *92*, 723–727.

5. Straathof, N. J. W.; Su, Y.; Hessel, V.; Noël, T. *Nature Prot.* **2016**, *11*, 10–21.

6. Dallinger, D.; Kappe, C. O. *Nature Prot.* **2017**, *12*, 2138–2147.

7. Flow chemistry education. http://futurechemistry.com/products-and-services/flow-chemistry-education/ (accessed November 28, 2017).

8. Support for flow chemistry education. https://www.vapourtec.com/products/e-series-support-for-flow-chemistry-training-education-teaching/ (accessed November 28, 2017).

9. For an excellent review, see: Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Rev.* **2016**, *116*, 10276–10341.

10. (a) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166; (b) Twilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. *Nature Rev. Chem.* **2017**, *1*, 0052.

11. For a recent review, see: Gruber, P.; Marques, M. P. C.; O'Sullivan, B.; Baganz, F.; Wohlgemuth, R.; Szita, N. *Biotechnol. J.* **2017**, *12*, 1700030.

12. *Flash Chemistry: Fast Organic Synthesis in Microsystems* Yoshida, J.; Wiley, New York, 2008.

13. Hessel, V.; Kralisch, D.; Kockmann, N.; Noël, T.; Wang, Q. *ChemSusChem* **2013**, *6*, 746–789.

14. ECHONET ITN. https://sites.google.com/a/sheffield.ac.uk/echonet-itn/ (accessed November 28, 2017).

15. (a) *Flow Chemistry* Darvas, F.; Hessel, V.; Dorman, G., Eds.; DeGruyter: Berlin, 2014, Vol. 1, Fundamentals; (b) *Flow Chemistry* Darvas, F.; Hessel, V.; Dorman, G., Eds.; DeGruyter: Berlin, 2014, Vol. 2, Applications.