

A Pioneering Early Microreactor Concept for Ultrafast Nitration Reactions — Placing the Seminal Brennecke and Kobe 1956 Contribution into Perspective

David Cantillo

Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010, Graz, Austria

During the past decade, the use of continuous-flow microreactors for organic synthesis has been growing dramatically [1, 2]. With the rapid development of microreactor technology, an increasing number of fine chemicals, traditionally prepared using batch or semibatch reactors, are now produced by continuous-flow methods [1]. Continuous-flow manufacturing, which has been classically associated almost exclusively with the oil and petrochemical industry, is becoming increasingly important in more complex organic syntheses and the preparation of pharmaceutical compounds and agrochemicals. The virtually instantaneous mixing achievable in microreactors, in addition to their characteristic exceptionally fast heat and mass transfer, makes this technology advantageous in particular for very fast and highly exothermic reactions [2]. Thus, reactions involving hazardous reagents or intermediates, or those in which high amounts of energy are released, can be performed in a safer and more controllable manner under flow conditions, microreactors thus being regarded as “intrinsically safe” [3, 4]. Some of the most dangerous processes in the chemical industry are nitration reactions. Nitrations are typically very exothermic and difficult to control on a large scale, and moreover, nitration products are often temperature- and friction-sensitive explosive compounds [5]. It is therefore not surprising that nitration reactions have benefited tremendously from the advantages provided by microreactor technology [6]. In 2005, Ducry and Roberge demonstrated that using microreactor technology dramatically enhances the selectivity and process safety, even during autocatalytic nitrations such as the nitration of phenols [7]. Nitration processes under very drastic conditions can also be performed in a safe and controllable manner [8]. There are a considerable number of continuous nitrations (especially for the preparation of nitroarenes) reported in the literature, as well as commercial scale plants in operation [3, 6]. Impressive production scale examples include a microreactor system for the continuous production of around 10 kg/h of nitroglycerin [9], or the formation of a nitrate-building block in the synthesis of naproxen, an anti-inflammatory drug with a total capacity of approximately 100 kg/h, by DSM [10]. Some early reports describing nitrations of bulk chemicals in continuous-flow mode appeared in the mid-20th century mainly due to the existing limitations for the size of chemical reactors [11]. Important examples are the Schmidt–Meissner process for the nitration of glycerol [12] or the production of 1,2-dinitropropane [13]. Levy and coworkers described the nitration of benzene using a small scale stirred-tank reactor [14]. It is not, however, until the beginning of the 21st century when miniaturized reactors (microreactors) have been perceived to have made their entry into the development of continuous-flow arene nitrations [6], with important contributions to the field from the groups of Loebbecke [15] or Roberge [7, 16], among others.

Within this context, we believe that the pioneering research by Brennecke and Kobe [17] has received too little or no attention in the recent flow literature. In 1956, these authors reported the mixed acid nitration of toluene in a miniature continuous-flow reactor from which useful kinetic data could be obtained for this very fast transformation. Their microreactor consisted of a 0.5-inch 304 stainless steel chamber with a small turbine-type stirrer in which toluene and a sulfonitric mixture were injected via two separate feeds. The volume of the reactor, taking into account the stirrer and a probe for temperature monitoring, was of ~1 mL. The system incorporated a water stream with the dual-purpose of cooling the reactor and quenching the reaction mixture immediately in the reactor output (Figure 1). The two reactants were pushed through the tubing into the microreactor with an air-pressure drive. The flow rate of the two liquid streams was monitored using two separate rotameters and controlled with needle valves installed in the rotameters output. Notably, using this continuous-flow setup, residence times (and hence reaction times) for the nitration as short as ~0.01 s could be achieved. The quenched biphasic mixture collected from the reactor output could then be easily separated and analyzed. With the lab equipment available at that moment, the study of reaction kinetics was typically limited to slow reaction rates. Kinetic data of highly exothermic reactions such as nitrations were not possible to obtain because the lab reactors could not release the heat of the reaction rapidly enough. Brennecke and Kobe realized and remarked that “the simplest way to increase the heat transfer is to increase the ratio of area to volume of the reactor by making it as small as possible” [17] (microreactor). Problems associated with biphasic mixtures and the importance of efficient mixing achievable in the microreactor for this type of fast transformations were also observed. This “quenched” continuous-flow reactor extended the available kinetic data for the nitration of toluene to rates a thousand-fold larger than those previously reported, and significantly contributed to the understanding of the nitronium ion mechanism.

The flourish of microreactor technology over the past decade has revealed very interesting applications for organic chemistry, especially for reactions in which high amounts of energy are released, and the efficient heat/mass transfer of microreactors plays a crucial role. This rapid progress has been possible to developments in other areas such as electronics, miniaturization, and engineering. The benefits of microreactors for harnessing this type of hazardous chemistries are now well established both in academy and industry. Despite the attention gathered by this technology in recent years, groundbreaking research using exactly the same physical principles (i.e., high surface to volume ratio, efficient mixing) such as the example from Brennecke and Kobe described herein made an important contribution to the field of flow chemistry and deserves recognition.

* Author for correspondence: david.cantillo@uni-graz.at

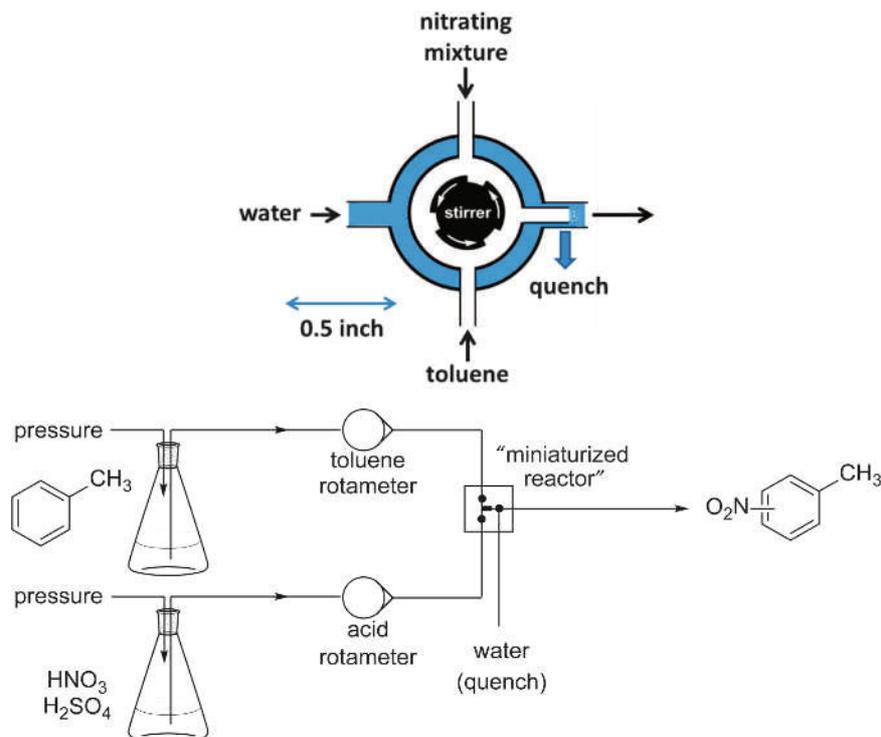


Figure 1. Schematic diagram of the microreactor and the continuous-flow setup utilized for the nitration of toluene

References

- (a) Malet-Sanz, L.; Susanne, F. *J. Med. Chem.* **2012**, *55*, 4062–4098; (b) Poehlauer, P.; Colberg, J.; Fisher, E.; Jansen, M.; Johnson, M. D.; Koenig, S. G.; Lawler, M.; Laporte, T.; Manley, J.; Martin, B.; O’Kearney-McMullan, A. *Org. Process Res. Dev.* **2013**, *17*, 1472–1478; (c) Thayer, A. M. *Chem. Eng. News* **2014**, *92*, 13; (d) Poehlauer, P.; Manley, J.; Broxterman, R.; Gregertsen, B.; Ridemark, M. *Org. Process Res. Dev.* **2012**, *16*, 1586–1590; (e) Jiménez-González, C.; Poehlauer, P.; Broxterman, Q. B.; Yang, B.-S.; Ende, D. A.; Baird, J.; Bertsch, C.; Hannah, R. E.; Dell’Orco, P.; Noorman, H.; Yee, S.; Reintjens, R.; Wells, A.; Massonneau, V.; Manley, J. *Org. Process Res. Dev.* **2011**, *15*, 900–911.
- (a) *Flow Chemistry*; Darvas, F.; Hessel, V.; Dorman, G., Eds.; De Gruyter: Berlin, 2014; (b) *Microreactors in Preparative Chemistry*; Reschetilowski, W., Ed.; Wiley-VCH: Weinheim, 2013; (c) *Microreactors in Organic Synthesis and Catalysis, 2nd Ed.*; Wirth, T., Ed.; Wiley-VCH: Weinheim, 2013; (d) *Handbook of Micro Reactors*; Hessel, V.; Schouten, J. C.; Renken, A.; Wang, Y.; Yoshida, J.-i., Eds.; Wiley-VCH: Weinheim, 2009; (e) *Chemical Reactions and Processes under Flow Conditions*; Luis, S. V.; Garcia-Verdugo, E., Eds.; RSC Green Chemistry: Cambridge, UK, 2010.
- Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688–6728.
- (a) Klais, O.; Westphal, F.; Benaissa, W.; Carson, D. *Chem. Eng. Technol.* **2009**, *32*, 1831–1844; (b) *ibid.* *Chem. Eng. Technol.* **2009**, *32*, 1966–1973; (c) Klais, O.; Westphal, F.; Benaissa, W.; Carson, D.; Albrecht, J. *Chem. Eng. Technol.* **2010**, *33*, 444–454; (d) Klais, O.; Albrecht, J.; Carson, D.; Kraut, M.; Lö, P.; Minnich, C.; Olschewski, F.; Reimers, C.; Simoncelli, A.; Uerdingen, M. *Chem. Eng. Technol.* **2010**, *33*, 1159–1168.
- Barton, J.; Rogers, R. *Chemical Reaction Hazards*, IChemE: Trowbridge, 1997.
- Kulkarni, A. A. *Beilstein J. Org. Chem.* **2014**, *10*, 405–424.
- Ducry, L.; Roberge, D. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7972–7975.
- Löwe, W.; Wie, G.; Jiang, M.; Hofmann, C.; Kost, H.-J.; Schütt, C. *Green Process Syn.* **2012**, *1*, 439–448.
- Thayer, A. M. *Chem. Eng. News* **2005**, *83*, 43.
- (a) Braune, S.; Pöchlauer, P.; Reintjens, R.; Steinhöfer, S.; Winter, M.; Lobet, O.; Guidat, R.; Woehl, P.; Guerneur, C. *Chim. Oggi/Chem. Today* **2009**, *27*, 26; (b) Thayer, A. M. *Chem. Eng. News* **2009**, *87*, 17.
- deC. Crater, W. *Ind. Eng. Chem.* **1948**, *40*, 1627–1635.
- Duehr, J. Nitration Technology for Aromatics as Described in the Patent Literature. In *Chemistry, Process Design, and Safety for the Nitration Industry*, ACS Symposium Series; American Chemical Society: Washington, DC, 2013; vol. 1155, pp. 71–82.
- Denton, W. I.; Bishop, R. B.; Nygaard, E. M.; Noland, T. T. *Ind. Eng. Chem.* **1948**, *40*, 381–384.
- Othmer, D. F.; Jacobs Jr., J. J.; Levy, J. F. *Ind. Eng. Chem.* **1942**, *34*, 286–291.
- (a) Antes, J.; Boskovic, D.; Krause, H.; Loebbecke, S.; Lutz, N.; Tuercke, T.; Schweikert, W. *Chem. Eng. Res. Des.* **2003**, *81*, 760–765; (b) Antes, J. T.; Marioth, E.; Schmid, K.; Krause, H.; Loebbecke, S. *Int. Microreactor Tech. Symp. (IMRETA)*, 2000; p. 194.
- (a) Kockmann, N.; Roberge, D. M. *Chem Eng Technol.* **2009**, *32*, 1682–1694; (b) Roberge, D.; Ducry, L. *Nitration of activated aromatics in microreactors*. WO2007/087816 A1, Aug 9, 2007.
- Brennecke, H. M.; Kobe, K. A. *Ind. Eng. Chem.* **1956**, *48*, 1298–1304.