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Reaction Screening Using a Microreactor

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Abstract: This article discusses the screening of chemical reactions using a microreactor equipped with infrared spectroscopy as online analytics. An esterification reaction has been optimized in continuous mode with the proposed setup. The esterification did not work well due to the material of the microreactor (stainless-steel 316Ti) that catalyzed the decomposition of formic acid. However, despite the occurrence of decomposition, an optimization could be achieved with this system.

Keywords: Continuous mode · Esterification · Microreactor · Optimization · Screening

1. Introduction

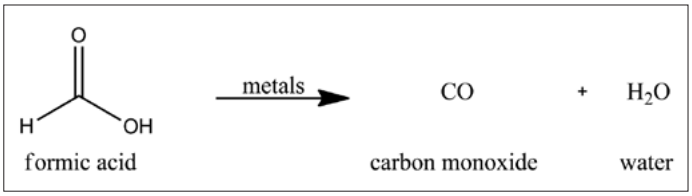
Our world has limited resources and a population that continually increases. Sustainable development is the main key to success for the future in the 21st century. Chemistry must play a central role in this process. In this context, only optimized chemical processes which have reached a maximum efficiency will lead to more sustainable products and production. Developing new chemicals implies, in an early step, an analysis of different parameters to be used during the optimization phase. A fundamental challenge in organic chemistry is to understand the reaction mechanism. In order to obtain this information, the chemical kinetics, including the reaction order and the rate constants, must be determined through experimentation.

The determination of the reaction mechanism requires intensive testing in the laboratory. Today, the chemist often uses an automated parallel system to collect data. The fed-batch mode is most often chosen to carry out the reaction. Its advantage is the flexibility during the introduction of the reactants and the possibility to work with solids, liquids or gases. The transfer from a fed-batch process to continuous mode is often difficult. Nevertheless the continuous mode has numerous advantages over fed-batch such as the possibility to work under steady-state conditions. This results in the possibility to adapt and control parameters, which facilitates the extraction of useful information. Using a tubular continuous microreactor with a small volume, a high heat transfer capacity and advanced automation possibilities presents significant benefits. Efficient screening of chemical reactions using fed-batch or continuous processes attempts to minimize:

– manpower,
– contact of laboratory personnel with chemicals,
– screening time, and
– quantity of chemicals used.

The use of a fully-automated microreactor[1] equipped with online analytics and software specifically designed for screening of chemical reactions should provide answers to these questions. This paper is based on the Bachelor thesis of Mathieu Roch.[2]

Scheme 1. Esterification reaction between formic acid and methanol.



Scheme 2. Probable decomposition reaction of formic acid in presence of metals.

2. Reaction

Scheme 1 shows the esterification reaction between formic acid and methanol, producing methyl formate and water, as tested by Droz.[3] In a typical case (fed-batch process), the water is distilled off during the reaction to move the equilibrium to the right. In the present case, due to the use of a microreactor made of stainless steel, the potential metal-catalyzed decomposition of formic acid must be considered. Scheme 2 presents this decomposition to produce water and carbon monoxide.

3. Experiment Setup

The setup presented in Fig. 1 can be divided into three main parts: the pumps, the microreactor, and the infrared spectrophotometer.

Two different pumping systems have been used with this installation. The first system was formed by two MZR 7208X1 S pumps from LEWA able to work in a range from 0.048 to 288 ml/min. The second system is made with two Encore™ HPLC pumps from Zymark functioning between 0.1 and 5 ml/min. The exact added mass was measured with two lab balances (Mettler-Toledo GmbH PR5002) placed upstream.

The microreactor used in the present study is an Ehrfeld system (Ehrfeld Mikrotechnik BTS, Wendelsheim, Germany) formed of an A3 clamping device, a slit plate mixer LH 25 (655 μl) with a temperature sensor, a Meander reactor (11.3 ml) thermostated with a Julabo oil bath (20 °C to 100 °C), a coaxial heat exchanger (620 μl) also connected to a second Julabo MV oil bath, and connection modules from Ehrfeld and from the Swagelok company.

The infrared spectra are realized with a PerkinElmer Spectrum 100 FTIR spectrophotometer including an ATR probe (Pike

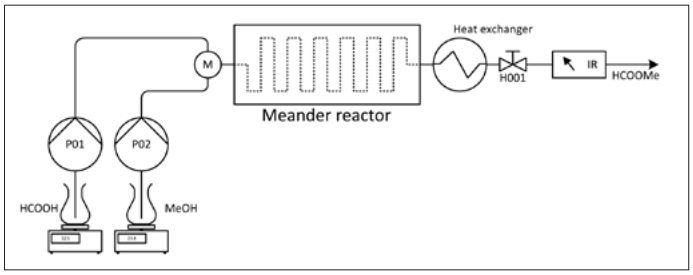


Fig. 1. Scheme of the microreactor used including the two pumps, the mixer, the Meander reactor, the heat exchanger, and the infrared spectrophotometer.

GladiATR) and a flow cell. A Mettler-Toledo React-IR can also be connected to this setup through a homemade flow cell.

4. Screening Methodology

In order to analyze the kinetics of the reaction, the concentration of the species at different times must be measured. With the reaction being carried out in a continuous tubular microreactor (assumption of a plug flow reactor – Reynolds number below 1'500), the flow rate of each pump can be modified to obtain different residence times. The concentration profile in the outflow as a function of the residence time can then be compared to the concentration profile of the same reaction implemented in a batch reactor. One possibility in order to use such a tubular microreactor to screen conditions is to test systematically a large set of feasible flow rates in the range allowed by the setup. Another option is to use a design of experiments strategy. The second method has been used in the present study, based on a Central Composite Face-centered (CCF) experimental design.[4] The CCF design, for three parameters, can be represented by a cube. The parameters are chosen on the extremes of the cube edge (corresponding to the maxima and minima of each parameter), at the center of each side, and at the middle of the cube. This method can be used not only for the determination of kinetic parameters but also to achieve a reaction optimization (yield and selectivity). The design of experiments strategy can also be used to analyze the correlation between the parameters.

Infrared spectroscopy was used to retrieve the concentration of the species for the esterification reaction. The Beer-Lambert law described for example by Stuart,[5] applied to the spectral information (matrix **D**), approximates the spectrum to a linear combination of the pure infrared spectra (matrix **S**) multiplied by the molar concentration (matrix **C**).

$$\mathbf{D} = \mathbf{C} \cdot \mathbf{S}^T$$

Using multiple linear regression (MLR),[6] the estimated concentration **C** can be retrieved by setting the error (**E**) to **0**. This estimation corresponds to a multiplication of the data matrix (**D**) by the pseudo-inverse matrix of the pure infrared spectra (**S**).

$$\mathbf{C} = \mathbf{D} \cdot (\mathbf{S}^T)^+$$

Advanced chemometric methods[7] give more robustness in the concentration estimation. The Multivariate Curves Resolution (MCR)[8] is implemented in our screening technique.

In order to study the kinetic behavior of the reaction, a kinetic model was implemented. With the assumptions that the tubular microreactor can be represented by a perfect plug flow reactor and that the mixture is in a single phase with a constant heat capacity (c_p) and density (ρ) and in isothermal conditions, the model is given by the partial mass balances for each species. As an example, for the esterification reaction of formic acid and methanol to methyl formiate and water,[9] the model is based on the following system of five differential equations.

$$\begin{aligned}
u \cdot \frac{d[\mathrm{HCOOH}]}{dz} &= -k_1 \cdot [\mathrm{HCOOH}] \cdot [\mathrm{MeOH}] + k_{-1} \cdot [\mathrm{H_2O}] \cdot [\mathrm{HCOOMe}] - k_2 \cdot [\mathrm{HCOOH}] \\
u \cdot \frac{d[\mathrm{MeOH}]}{dz} &= -k_1 \cdot [\mathrm{HCOOH}] \cdot [\mathrm{MeOH}] + k_{-1} \cdot [\mathrm{H_2O}] \cdot [\mathrm{HCOOMe}] \\
u \cdot \frac{d[\mathrm{H_2O}]}{dz} &= +k_1 \cdot [\mathrm{HCOOH}] \cdot [\mathrm{MeOH}] - k_{-1} \cdot [\mathrm{H_2O}] \cdot [\mathrm{HCOOMe}] + k_2 \cdot [\mathrm{HCOOH}] \\
u \cdot \frac{d[\mathrm{HCOOMe}]}{dz} &= +k_1 \cdot [\mathrm{HCOOH}] \cdot [\mathrm{MeOH}] - k_{-1} \cdot [\mathrm{H_2O}] \cdot [\mathrm{HCOOMe}] \\
u \cdot \frac{d[\mathrm{CO}]}{dz} &= +k_2 \cdot [\mathrm{HCOOH}]
\end{aligned}$$

where k_{+1} is the kinetic constant of the forward reaction of esterification in L/(mol·s^{-1}), k_{-1} is the kinetic constant of the backward reaction of esterification in L/(mol·s^{-1}), k_2 is the kinetic constant for the decomposition of the formic acid in 1/s^{-1}, [HCOOH] is the molar concentration of the formic acid, [MeOH] is the molar concentration of the methanol, [HCOOMe] is the molar concentration of the methyl formiate, [H_2O] is the molar concentration of water, [CO] is the molar concentration of carbon monoxide, u is the linear velocity of the fluid in m/s, and z the position in the tube in m.

Due to the decomposition reaction of formic acid, the assumptions about the monophasic system and a constant density are not respected. However, more complex models are not discussed here. The minimization of the error function between the model and the data is based on the Nelder-Mead method using the principle of the Simplex. The method works iteratively as described by Mathews and Fink.[10]

5. Results and Discussion

The concentrations calculated with the online infrared spectrophotometer are based on a limited region of the spectra (between wavenumbers of 450 cm^{-1} and 1'500 cm^{-1}). These values have been validated with Nuclear Magnetic Resonance (NMR) analysis. The measurement error is approximately 5% between the two methods. The points measured at approximately 44 °C are used to determine the kinetics constants. The values are: k_{+1} = 2·10^{-4} mol·l^{-1}·s^{-1}, k_{-1} = 5·10^{-4} mol·l^{-1}·s^{-1}, and k_2 = 3·10^{-3} s^{-1}. Fig. 2 shows the comparison between the measured data and the simulation based on the calculated kinetics constants. The observed difference between the measured data and the simulated data can be explained with the unexpected decomposition of formic acid. The proposed model does not include the two phase (gas/liquid) system. Fig. 3 presents a comparison between the batch reaction and the continuous reaction. The batch reaction is carried out in a glass vessel which prevents decomposition.

6. Conclusion

This work highlights the role played by the metal-catalyzed decomposition of formic acid in the esterification reaction between formic acid and methanol. The continuous implementation of this reaction in an automated tubular microreactor provides estimates of the kinetic parameters. The precision of these estimates could be increased by measuring the concentrations at a wider range of flow rates. The proposed methodology provides a

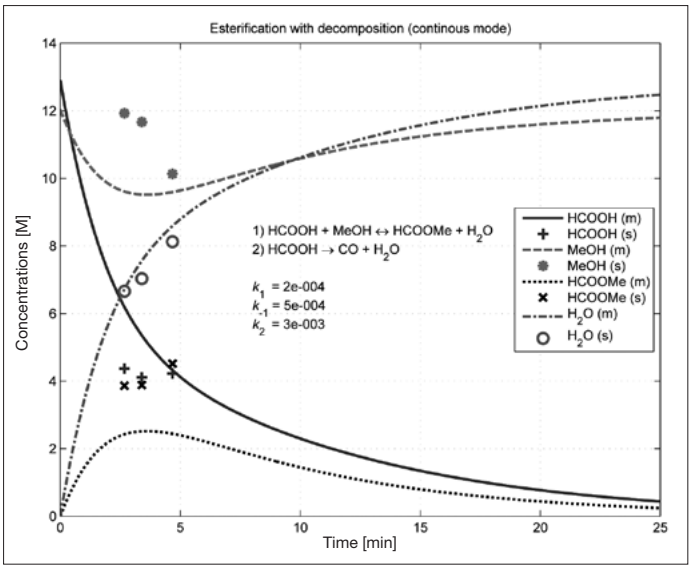


Fig. 2. Comparison between the measured data and the simulation for the esterification reaction in the tubular microreactor.

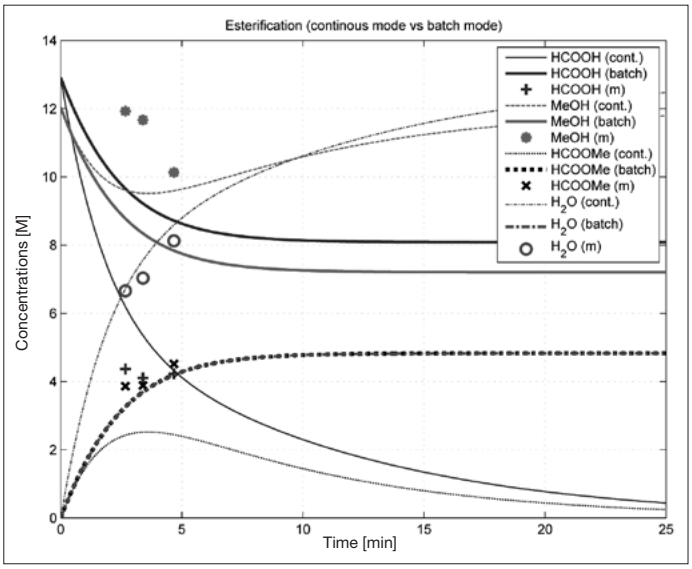


Fig. 3. Comparison between the esterification reactions carried out in a glass vessel (batch mode) and in the metal Ehrfeld reactor (continuous mode).

reaction screening platform that requires minimal personnel and material resources.

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Information

News – Honors – Workshops – Conferences – Lectures

HONORS

Professor ***Stefan Willitsch*** of University Basel received the Ruzicka-Award 2010 on November 29th, 2010 at the ETH Zurich for his work in the field of producing and trapping ultracold ions and the investigation of chemical processes at extremely low temperatures.

The European Society for Molecular Biology acknowledged the outstanding Achievments of ***Yves Barral*** and ***Ulrike Kutay***, both Professors at the Institute for Biochemistry, ETH Zurich, and ***Rudolf Glockshuber***, Professor for Molecular Biology, ETH Zurich, by affiliating them as members.

Professor ***Raffaele Mezzenga***, Institute of Food Sciences, ETH Zurich, has been awarded the John H. Dillon Medal 2011, which honors distinguished research in the field of polymer physics. He was elected for his extraordinary contributions to the principles of self-assembly and their application to development and control of functional materials.

NEWS

Vahid Sandoghdar, Professor am Laboratorium für Physikalische Chemie der ETH Zürich, verlässt die ETH. Er folgt dem Ruf einer Humboldtprofessur an die Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg und wird zudem Direktor des Max-Planck-Instituts (MPI) für die Physik des Lichts werden.

CONFERENCES/WORKSHOPS/SYMPOSIA

SAOG 2011: 27th Annual Meeting of the Swiss Working Group for Surface and Interface Science (SAOG)

Topic: Interfacial Science in Energy Conversion and Storage, January 28th 2011, at the Université de Fribourg, Département de Physique, Chemin du Musée 3 CH-1700 Fribourg, see *www.saog-gssi.ch* for details.

C4 Workshop: Advancing the Frontiers of Modeling and Simulation in Chemistry and Material Science. January 13, 2011, 09:00–17:30

IBM Research Laboratory, Rüschlikon

LECTURES

Departement Chemie der Universität Basel
Anorganische und Organische Chemie

Departement Chemie, Universität Basel, kleiner Hörsaal Organische Chemie, St. Johanns-Ring 19, CH-4056 Basel

17.12.2010 Freitag 10.45 h	Prof. Dr. *A. Ganesan* University of Southampton, UK 'Natural, artificial and imaginary approaches to drug discovery'
26.1.2011 Mittwoch 10.45 h	Prof. Dr. *Yujiro Hayashi* Tokyo University of Science, Japan Title to be announced
23.2.2011 Mittwoch 17.30 h	Prof. Dr. *Mark Lautens* University of Toronto, Toronto, Canada Title to be announced

Departement Pharmazeutische Wissenschaften der Universität Basel

Pharmazentrum, Klingelbergstrasse 50, 4056 Basel Hörsaal 1
Mittwochs, 17.00 h

15.12.2010	Dr. *Hugo Kupferschmidt* Schweiz. Toxikologisches Zentrum Zürich Title to be announced
22.12.2010	Dr. *Hanns-Christian Mahler* F. Hoffmann-La Roche Ltd. 'Biopharmaceuticals'

Département de Chimie organique, Université de Genève

Sciences II, Quai Ernest-Ansermet 30, Genève

16.12.2010 Jeudi Time tba	Dr. *A. Ganesan* University of Southampton, U.K. 'Natural Products, Unnatural Analogues and Virtual Compounds : Three Pathways to Biological Activity'
13.1.2011 Jeudi 16.30 h	Dr. *Frederic Leroux* Directeur de recherches CNRS 'The 'ARYNE'-Coupling : A Key-Reaction in the Synthesis of New C1 Symmetric Biarylligands'
20.1.2011 Jeudi 16.30 h	Prof. *Francesco Stellacci* Department of Materials Science and Engineering EPFL, Switzerland and MIT, Cambridge, MA, USA 'Supramolecular Nanotructure Surfaces: From Membrane Penetration to Ion Sensing'
3.2.2011 Jeudi	Prof. *Jieping Zhu* CRNS and EPFL 'Rapid Access to Heterocycles by Palladium-Catalyzed Domino Process'
17.2.2011 Jeudi 16.30 h	Prof. *Pierangelo Metrangolo* Department of Chemistry, Materials, and Chemical Engineering 'G. Natta' Politecnico di Milano Milan, I 'Halogen vs. Hydrogen in Anion Binding Interactions'

Institut Pharmazeutische Wissenschaften der ETH Zürich

Universität Zürich, Campus Irchel, Y17 M05
Mittwoch, 17.15 h

15.12.2010	Prof. Dr. *Frank Heppner* Charité Berlin 'Neuroimmune actions in Alzheimer's disease'

Organisch-chemisches Institut der Universität Zürich

ETH Zürich, Rämistrasse 101, 8092 Zürich, HG F 30
Montag, 17.15 h

20.12.2010	Prof. Dr. *Shana J. Sturla* Institut für Lebensmittelwissenschaften, Ernährung und Gesundheit, ETH Zürich 'The Diet-Cancer Connection at Chemical Resolution'

Physikalisch-chemisches Institut der Universität Zürich

Seminarraum 34-K-01, Winterthurerstrasse 190, Universität Zürich-Irchel
Donnerstag, 10.15 h

16.12.2010	Prof. Dr. *Jürgen Brugger* Institute of Microengineering, EPFL Lausanne 'Nanostencil lithography as versatile surface patterning method'