CHEMICAL ENGINEERING TRANSACTIONS

VOL. 29, 2012

A publication of
AIDIC
The Italian Association
of Chemical Engineering
Online at: www.aidic.it/cet

Guest Editors: Petar Sabev Varbanov, Hon Loong Lam, Jiří Jaromír Klemeš

ISBN 978-88-95608-20-4; **ISSN** 1974-9791

DOI: 10.3303/CET1229167

Reconnaissance of Reaction Networks and Kinetics by New Combination of Analytical Techniques

Oliver Litzmann*[a], Thomas Grützner[b], Tobias Merz[b], Constanze Müller [d], Günter Wozny[a], Jens-Uwe Repke[c]

[a]Berlin Institute of Technology, Sekr. KWT-9, Strasse des 17. Juni 135, 10623 Berlin, Germany
[b]Lonza AG, Lonzastrasse, 3930 Visp, Switzerland
[c]Technical University of Freiberg, Institute for Thermal, environmental and Natural Products Process Engineering, Leipziger Strasse 28, 09596 Freiberg, Germany
[d] formerly Lonza AG, Lonzastrasse,3930 Visp
*oliver.litzmann@tu-berlin.de

The proper description of reaction networks and the underlying reaction kinetics are crucial points for the design of new chemical processes. Even in the case of well known reaction mechanisms, the solvents or side products may have significant influence on the reaction path and kinetic.
This paper describes an industrial relevant reaction for which preliminary investigations have revealed a system of reactants and solvent that is leading to a satisfactory yield. In order to scale up a reactor concept the reaction path and kinetic had to be explained. Therefore a method was developed which combines online-Raman-spectroscopy with offline quantitative nuclear magnetic resonance measurements for the hydrogen atoms (^{1}H-QNMR). Combining these methods and using statistical methods like principal components analysis an autocatalytic effect could be detected and described in the reaction model. The model parameters are fitted to the experiments so the model can be used for the scale up from the lab scale.
The paper presents the experimental set-up as well as the mathematical development of the reaction model.

1. Introduction

The reaction investigated is a nucleophile substitution as shown in *Figure 1.* The leaving group X at the alpha position shall be substituted by the stronger nucleophile Y. Y is added in the form of its weak acid so an additional base has to be used in order to support the dissociation into a proton and the reactive ion Y^-. The acid / base ratio used is crucial for the yield of the reaction as a high pH value leads to side-reactions where both esters form a dimer or even a trimer. On the other hand, high concentrations of HY may form other undesirable sideproducts. While the formation these products can be avoided by the reaction condition, the di- and trimeric esters are inevitable produced in small amounts which needs to be represented in the kinetic model.
The usage of an aprotic solvent with average polarity and the absence of sterical interference at the alpha carbon atom indicates, that the reaction should be describable by a second order reaction according to the S_N2 reaction mechanism.

Please cite this article as: Litzmann O., Grützner T., Merz T., Mueller C., Wozny G. and Repke J.-U., (2012), Reconnaissance of reaction networks and kinetics by new combination of analytical technique, Chemical Engineering Transactions, 29, 997-1002

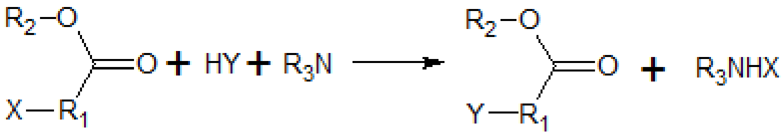

Figure 1: Reaction scheme for the investigated SN reaction where R1, R2 and R3 represent aliphatic chains, X represents the leaving group and HY the still bounded nucleophile.

Nevertheless in preliminary investigations using reaction calorimetry it was neither possible to describe the results by a second order nor a first order kinetic approach. Consequentially none of the standard reaction mechanism for SN reactions seems to be able to describe the investigated reaction. Therefore spectroscopic methods should be used in order to clarify the effects which differ from the standard mechanisms.

Different methods for online spectroscopy are described in literature. The most common technique for kinetic investigations is the fourier transformed infrared spectroscopy (FTIR) which is available since 1970 and is likely combined with reaction calorimetry (e.g. Bundschuh, 2004)**.** Raman spectroscopy on the other hand uses a vibration effect as well and complements IR spectroscopy due to another exciting mechanism so that one chemical group is either IR active or Raman active. As the Raman emitted radiation is (Chalmers and Dent, 1997) orders of magnitudes smaller then the effect measured in IR spectroscopy, Raman measurements took a longer period to develop and are applied in less cases then FTIR. In the present case the resolution of Raman measurements was higher and the peaks do not overlap as much as using IR. Another argument for the use of Raman is the excited material which is a true volume in case of Raman measurements but only the contact area between probe head and reaction phase in case of FTIR. This needs to be taken into account for reactions with more than one phase or high variations in local compositions.

As another spectroscopic method nuclear magnetic resonance spectroscopy needs to be mentioned which has been applied for long time for the reconnaissance of chemical structures and recently for online measurements of kinetic reactions as well (Grützner, 2007)**.** Combinations of Raman and NMR measurements have been reported so far (Carvalho et al., 2006), where different properties of reaction products were measured using different analytical methods.

2. Material and Methods

2.1 Experimental set-up

The experiments were carried out in a fully automated 0.6 L LabMax reactor purchased from Mettler Toledo. *Figure 2* shows a P&I diagram of the reactor with two scales for mass stream control and a cascade control for the reaction temperature. The reactor temperature is controlled by splitting the heating oil to an electrical heater and a sole cooler, so that a fast adjustment of the jacket temperature can be realised. Two mass flows can be added to the reactor by a combination of scales and pumps so that a semi batch mode is realisable with high accuracy. Besides the connections for the mass streams and the temperature sensor, a reflux cooler and the Raman probe head are installed at the reactor cap. In a typical achievement the starting ester is laid in the reactor and heated to reaction temperature while stirring. After reaching steady state a mixture of HY in a solvent is added in a first stream and pure R_3N as second stream. After both doses are completely added, the reactor is further stirred and kept on reaction temperature until no temperature difference between reactor and jacket is observed anymore. During the reaction the side product R_3NHX forms a solid as its solubility in the mixture is too low. In order to close the mass balance in a reliable manner some water is added to the reactor which solves the solid particles and forms a second liquid phase. The liquid phases are then discharged from the reactor and weighted separately. Sample from both phases are taken and analysed using ^{1}H-NMR. The chemicals used have been purchased by Sigma Aldrich or have been taken from own synthesis with a purity of > 99 %.

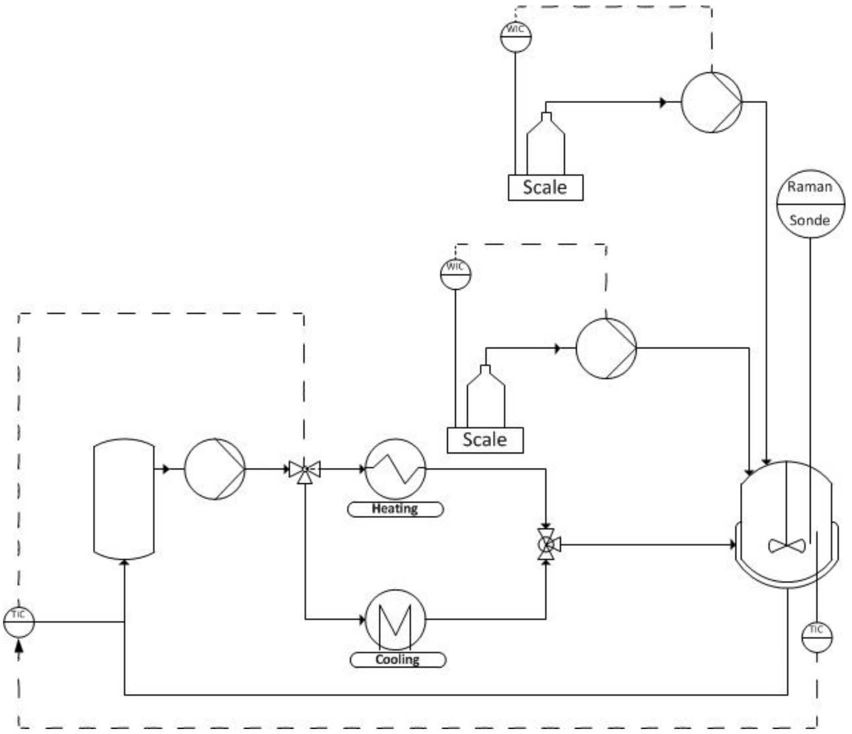

Figure 2: P&I Diagram of the LabMax reactor used for the experiments. The reactor temperature is used to define a set point for the jacket temperature which is controlled by a valve dividing the thermo oil to heating and cooling. A disturbance variable compensation is also possible but not shown here.

2.2 Raman Spectroscopy

For the Raman measurements a Kaiser Optical Systems RxN2 spectrometer was used which is a 4 channel dispersive spectrometer with CCD detector. As probe head a non-contact Immersion Optics head with 1/2'' diameter was applied. The spectrometer was controlled using Kaiser's ICRaman Software v.4.1.910.0. As exciting source a deep red laser with a wavelength of 785 nm was used. All spectra were recorded with a wavenumber resolution of 1 cm^{-1} in a spectral domain of 3425 cm^{-1} - 100 cm^{-1}. Every 30 s one spectrum was recorded.

In order to transform the recorded spectra into concentrations a calibration was needed. Therefore 18 non-reactive mixtures were produced and scanned using the set up as described and used for a partial least square regression to predict the concentrations during the reaction.

As Raman spectra often show high variation in absolute peak intensities (Mandall, 1999) all calibration spectra were normalized according to *equation 1* were k (1...M) means the number of measured wave numbers per spectrum and N means the number of the acquired spectra.

$$\bar{I}_{i,k} = I_{i,k} - \frac{1}{N}\sum_{i=1}^{N} I_{i,k} \tag{1}$$

These normalized spectra are then subjected to a principal component analysis (PCA) in which the data matrix X with the dimensions N x M is transformed into a new coordinates system of lower dimensions A. The aim of the PCA is a system in which the first coordinate describes a maximum of the original data's variance. The data described by the first new coordinate are deleted from the original data matrix, and a second new coordinate is build which describes the data with the highest variance of the remaining data. This results in an orthogonal coordinate system with A coordinates, in which the data matrix can be written as

$$\boldsymbol{X}\ (N\text{x}M) = \boldsymbol{T}\ (N\text{x}A) \cdot \boldsymbol{P}\ (A\text{x}M) + \boldsymbol{E}\ (N\text{x}M) \tag{2}$$

E includes the non-declared residuals and becomes smaller the higher the dimension A is chosen. This often leads to the so called overfitting meaning, the noise of the spectra is declared as well. The thoughtful choice of A is therefore the key to a good PCA. In order to calculate concentrations from new spectra, a model is build which uses a PCA of the calibration spectra and correlates them to a PCA of the known concentrations in the calibration samples. The calculations were done using the Software “The Unscrambler X” which was also applied generates the time vs. concentration plots for the reactions.

2.3 NMR

The ^{1}H-NMR measurements of both liquid phases of the fully reacted mixture was done using a Bruker AVANCE-III spectrometer with a exiting frequency of 400 MHz and therefore a magnetic field force of 9,4 Tesla. 20 mg of the sample substance was diluted in a mixture of DMSO-d$_6$ and trimethylsiloxane against which the chemical shifts were calculated. Additionally 20 mg of benzylbenzoate was added as internal standard. The spectra were measured at 20 °C using electric pulses with a duration of 15 µs and a power of 12 W. Eight free induction decay have measured with a delay time of 25 s. The spectra were analysed using ACD / NMR Processor by ACDLabs. Therefore the fid was Fourier transformed to the frequency domain. The phases and baseline were corrected using the software’s procedure. The peaks were picked and integrated manually. The calculation of the components weight percent was done using Eq 3. For all samples the concentrations were calculated using the CH$_2$ singlet at 5.36 ppm and the aromatic peaks between 8 and 7.3 ppm of the benzylbenzoate and were in good agreement. In order to minimize the error by sample preparation the samples were prepared and analyzed two times what gives 4 results for every concentration with a maximum standard deviation of 1 weight percent.

$$\xi_i = \frac{m_{\text{ISTD}} \cdot A_{\text{Peak}} \cdot M_{\text{i}} \cdot n_{\text{H}_{\text{ISTD}}}}{m_{\text{Sample}} \cdot A_{\text{ISTD}} \cdot M_{\text{ISTD}} \cdot n_{\text{H}_{\text{i}}}} \tag{3}$$

3. Experimental Results

Although the model used for the conversion from spectra to concentration has high regression coefficients, the predicted concentration shows some errors, e.g. negative values, or do not meet the results given by NMR. The reasons for this are e.g. the higher complexity in a multi component system comparing the non reactive calibration samples and the different particle size distribution of the solid particles, as the powder used for the calibrations of course varies from the particles produced in the reactor. As to the fit of the model parameters a reliable and realistic concentration trend is needed the concentrations predicted from the Raman measurements were corrected using the NMR results and initial conditions. These both reference conditions gave fixed points which had to be described by Raman. The Raman concentrations therefore were stretched and shrinked according to *equation 4* which simply compares the maximum concentrations differences for both methods and correlates them.

$$c_i^{\text{corr.}}(t) = \frac{c_i^{\text{Raman}}(t) - \min\{c_i^{\text{Raman}}\}}{\max\{c_i^{\text{Raman}}\} - \min\{c_i^{\text{Raman}}\}} \cdot \left(\max\{c_i^{\text{NMR}}\} - \min\{c_i^{\text{NMR}}\}\right) + \min\{c_i^{\text{NMR}}\} \tag{4}$$

Figure *3* shows the comparison between the concentration trend predicted by the Raman model and the NMR scaled trends. The concentration of the produced ester is in perfect agreement where the highest deviation is observed for the solid side product as presumed.

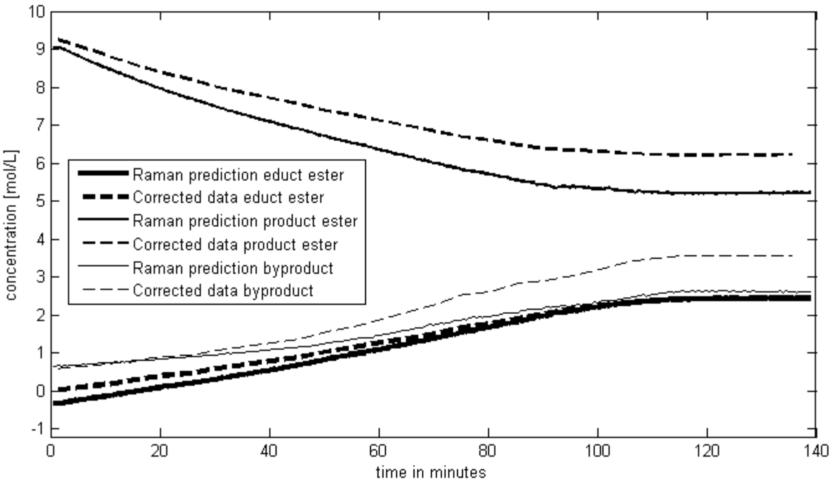

Figure 3: Comparison between the Raman predicted concentration trends and the trends scaled by NMR measurements for the both esters and the side product R_3NHX.

Besides the measurement of concentration trends, Raman spectroscopy allows to differentiate between two or more states of one component. In the present case it was possible to discriminate between the weak acid HY and the reactive ion Y^-. For this species no calibration could be done as no reliable reference method was available. Nevertheless it could be shown, that HY dissociates in a mixture of R_3NHX and an inert solvent which was not described before and needs to be taken into account for the kinetic model. As the base is still needed to catch the X^- ions the reaction does not start if HY and R_3NHX are mixed with the starting ester.

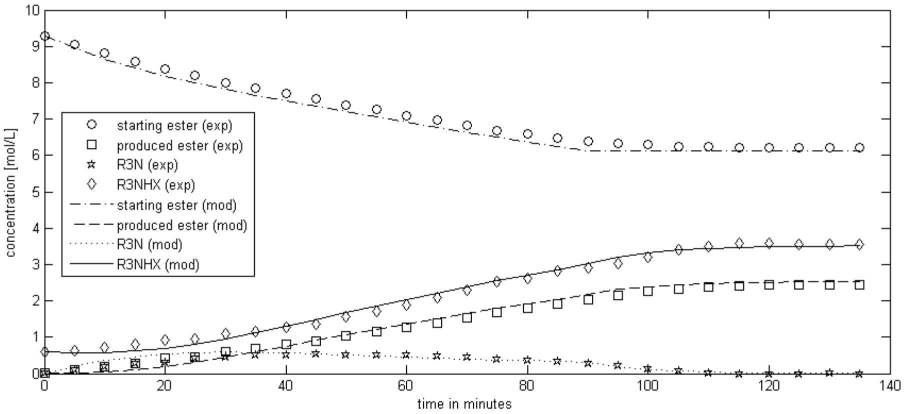

Figure 4: Comparison between the NMR corrected Raman trends and the complete reaction model

4. Reaction Modelling

As the reasoning for a bimolecular reaction according to the S_N2 mechanism is still valid this kinetic model had to be extended to the described dissociation effect. As the reactants in a S_N2 reaction are the ester and the reactive ion Y^- a description for the degree of dissociation was necessary. This dissociation could not be measured in any other way then with Raman spectroscopy, therefore the ratio peak heights of HY and Y^- was used as means to determine the degree of dissociation. It was found that the resulting values could be described by a bilinear equation using the concentrations of R_3N and

R_3NHX. The polynomial parameters were fitted to the investigated temperature levels and could be described in good agreement by an Arrhenius approach. In order to fit the kinetic parameters the reactions were simulated as systems of differential equations and solved using Matlab's Runge-Kutta algorithm. The deviation between model and experiments were calculated as sum of deviation's squares and minimized using a nonlinear Matlab solver. The model build describes the formation of dimeric ester although no Raman peak could be assigned to this component. Therefore the difference between the desired product and the side product R_3NHX can be used. The kinetic parameters were fitted at different temperatures and also could be represented by an Arrhenius approach. **Error! Reference source not found.** shows the NMR corrected Raman data from *Figure 3* in comparison to the trend calculated by the model. The results are in a very good agreement.

5. Conclusions

The measurement and modelling of a nucleophile substitution was addressed in the work presented. It was shown that even if the mechanism seems predictable various effects of the solvent and reaction matrix may influence the reaction mechanism respectively the degree of details which are needed for a proper description of the reaction kinetic. The concentrations during the reaction were measured by Raman spectroscopy which gave valuable information about the degree of dissociation by various effects. The degree of dissociation could be described by a semi-quantitative method whereby all other concentrations were calculated using multivariate methods such as PCA. A combination of NMR and Raman measurements was introduced in the work presented in order to correct the Raman measurement's errors due to particle size distribution and side products which were not calibrated. This new combination leaded to concentration results with high accuracy which allowed to fit the kinetic parameters of the extended reaction model which is also able to describe the amount of side products which were not measured as well. The model is able to describe the reaction in a temperature interval of 25 °C and describes various ratios of concentrations so it can be used in order to scale a reactor for larger amounts.

References

Bundschuh, M., 2004, Comparison of different methods of determination of the formal kinetics using reaction calorimetry and on-line FTIR sensor, PhD Thesis, Berlin Institute of Technology, Germany (in German)

Chalmers, J.M., Dent, G., 1997, Industrial analysis with vibrational spectroscopy, The Royal Society of Chemistry, Cambridge, United Kingdom

Grützner, T, 2007, Development of a distillation-based method for preparing trioxane, PhD Thesis, University of Stuttgart, Germany (in German)

Carvalho, L.M.H., Costa, M.R.P.F.N., Costa, C.A.V., 2006, A very simple empirical kinetic model of the acid-catalyzed cure of urea-formaldehyd resins, Journal of Applied Polymer Science, 102, 6, 5977-5987

Mandall, O., 1999, Creation and validation of a combined NIR / Raman library to check identity of organic and inorganic substances, PhD Thesis, Gerhard Mercator Universität – Gesamthochschule Duisburg, Germany (in German)