

Online Spectroscopic Investigations (FTIR/Raman) of Industrial Reactions: Synthesis of Tributyltin Azide and Hydrogenation of Chloronitrobenzene

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Abstract:

The utilization of online spectroscopic methods (FTIR/Raman) for the development and the monitoring of chemical processes was demonstrated with two important chemical reaction types. The synthesis of tri-*n*-butyltin azide takes place at the solid–liquid interface and is therefore very sensitive to changes of reaction conditions or surface properties. Traditional offline analysis should be avoided due to the high toxicity of the compounds. The concentration variations of all involved compounds were determined. In the same way, the synthesis of 2-chloroaniline was studied to detect the formation of an unstable intermediate (the hydroxylamine) which can lead to uncontrolled decomposition reactions. Online spectroscopy is an opportunity to obtain the information about a reaction system faster and more efficiently than with conventional methods. This allows the rapid optimization of safe chemical processes and provides information for process control.

1. Introduction

Reaction monitoring is of central interest to chemists working in all stages of chemical development. It is an opportunity to obtain, much faster than usual, the information about a reaction system. This allows us to optimize chemical processes much faster and to use the information for the process control. Three main application fields of online analytics can be distinguished.

Reaction Analysis for Chemical R&D. (1) Determination of the chemical mechanism and pathway: online spectroscopy offers a mean to analyze reactions which have unstable intermediates or are run under conditions which prevent grab-sample analysis. For example, many reactions are run at -80 to 0 °C, and it is difficult to have a good method for tracking the process. Pulling a reaction sample destroys it, and it cannot be put on a LC column. (2) Measurement of real-time conversion data: these methods provide end point of a reaction, conversion, relative concentrations, and eventually absolute concentration data for a wide range of reactions. Therefore, they provide the basis for developing analytical methodology for process monitoring in a plant.

Reaction Engineering for Process R&D. (1) Process development and scale-up: when used in combination with

reaction calorimetry and simulation software, all necessary data for the process improvement and optimization can be obtained. (2) The effect of reaction variables on reaction performance can be determined. (3) Reduction of the development time: the majority of the used equipment (reaction calorimeter, spectrometer) can work fully automated (even overnight or during the week-end). This time gain can lead to a significant reduction of the time to market. (4) Finally, the combination of these methods ensures the development of a safe, optimized, and well-controlled process.

Process Monitoring for Manufacturing Efficiency. (1) Determination of the reaction completion (optimization of the cycle time, avoid unnecessary stirring periods, no sampling of toxic reaction mixtures for the traditional analytics). (2) Monitoring of process variance (e.g. control of the dosing feed of a reagent to avoid thermal accumulation).

2. Instruments

The FTIR spectroscopic online measurements were carried out with a ReactIR 1000 instrument (Applied Systems) equipped with a diamond probe. This spectrometer operates according to the Fourier transform method and utilizes the ATR principle (attenuated total reflection). Therefore, the penetration depth of the surface waves into the absorbing medium is very small. The spectral region comprises between 650 and 4000 cm^{-1} .

The Raman spectroscopic online measurements were carried out with HoloLab Series 5000 and HoloProbe VPT System (Kaiser Optical Systems, Inc.). These spectrometers use a fiber-optic cable and immersion probe with sapphire window to both deliver the excitation laser light to the reaction mixture and receive the light scattered back. The spectral region comprises between 50 and 3500 cm^{-1} .

3. Examples

Since characteristic differences of the vibrational spectra of starting material and product were expected, the progress of the reactions was followed by simultaneous in situ FTIR and Raman analysis. Both spectroscopic probes were installed in a RC1 reaction calorimeter. All signals were simultaneously recorded. The thermal data were used for the assessment of the thermal safety of the investigated reactions. Thermal analysis was not the goal of this study, and therefore these results are not discussed in this paper.

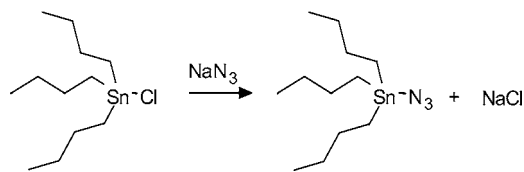
If no specific literature reference is mentioned for the evaluation of the spectroscopic data, the correlation between

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Scheme 1. Synthesis of tri-*n*-butyltin azide



the measured wavenumbers and the functional groups was determined from general spectroscopy books.^{1–3}

3.1. Synthesis of Tri-*n*-butyltin Azide. 3.1.1. Introduction. The goal of this study was to evaluate the potential of online spectroscopic tools for monitoring chemical processes and detecting deviations from nominal operating conditions. The literature-known synthesis of tri-*n*-butyltin azide from tri-*n*-butyltin chloride and sodium azide (Scheme 1) was studied as a model reaction.⁴

The principal industrial applications of trialkyltin compounds include biocides in marine antifouling paints, fungicides, herbicides, insecticides, miticides, and antifeedants in agriculture. Tri-*n*-butyltin azide is of some importance as a reagent for the preparation of pharmaceutical tetrazole compounds.^{5–7} Online monitoring of such a heterogeneous reaction system by spectroscopic methods may be advantageous for various reasons.

The reaction of crystalline sodium azide with liquid tri-*n*-butyltin chloride takes place at the solid–liquid interface and is therefore very sensitive to changes of reaction conditions or surface properties. Standard offline methods may be used to monitor reaction progress; however, they require repeated sample-taking and -handling during the analytic process. These operations should be avoided due to the high toxicity of the reaction mixture and also for reasons of safety and ecology.

All compounds involved in this reaction have low maximum allowed concentration (MAK) values. Organotin compounds have a wide range of toxicity, the most toxic being trialkyltins as evident from their broad spectrum of application as biocides. They are capable of blocking the oxidative phosphorylation in the mitochondria cell.⁸ Thus, they influence the basic energetic functions in living cell systems. Triorganotin compounds can react with active centers in the cell by forming coordinating links with amino acids of the cell proteins. Moreover, these compounds can cause severe skin irritation.⁹ Further, azides are highly poisonous and usually sensitive to traces of strong acids and metallic salts which may catalyze explosive decomposition. For example, the isolation of explosive silver azide must be avoided during the offline titration of the unreacted tri-*n*-butyltin chloride with silver nitrate.

The growing awareness of the environmental fate of organic tin compounds has reflected in the large number of analytical methods developed for their determination and specification.^{10,11} Most methods are too complex to be carried out routinely in a production plant (goal: determination of the completion of the reaction).

Finally, detailed knowledge of the reaction kinetics, as determined from continuous online measurements of reactant and product concentrations, may help to improve the reaction conditions and thus increases process safety.

3.1.2. Experimental Section. Tri-*n*-butyltin chloride was charged at room temperature in a stirred reactor, and the reaction system was inerted with nitrogen. Then, the contents of the reactor was heated to 50 °C. After a first calibration of the reaction calorimeter, sodium azide was added over 5 min. The reaction mixture was stirred during 21 h at the same temperature. After a repeat calibration, the reaction mass was cooled to 25 °C.

3.1.3. Results and Discussion. 3.1.3.1. Normalization of Spectra. Reaction profiles constructed from normalized spectra are less noisy. Therefore, trends are more easily recognizable and interpretable after normalization of the spectra. Normalizations can help correct fluctuations or systematic increases or decreases in peak intensity due to (i) variations in the amount, the composition, or the morphology of solid, crystalline materials in the reaction mixture; (ii) the temporary or permanent adherence of crystals or other particles to the diamond or the sapphire window of the probes; (iii) the temporary or permanent formation of thin films on the diamond window of the FTIR probe; or (iv) changes in the distance between the laser focal point and the sapphire window of the Raman probe.

Useful peaks for spectra normalizations are peaks resulting from solvent molecules or from functional groups which are located far away from the reaction centers of the molecules involved in the reaction. More general, any peak arising from species or functional groups which do not undergo any change in concentration or absolute mass and which can be regarded as constant is suited for a normalization. Furthermore, the selected peak ideally should be of medium intensity, i.e., still in the linear range, and located somewhere in the center of the observed spectral region or close to a region with significant changes or another region of particular interest.

The normalizations were carried out taking the region 1110.6–1221.1 cm^{-1} (τCH_2 and ωCH_2) for the Raman spectra and the region 815–910 cm^{-1} (ρCH_2 and ρCH_3) for the FTIR spectra, i.e., the spectra were stretched or compressed so that the peak maxima and the baselines of all the spectra attained maximum overlap in these regions.

3.1.3.2. Raman Data. The most important changes in the Raman spectra are summarized hereafter (see Figures 1–3):

- (1) Socrates, G. *Infrared Characteristic Group Frequencies*; Wiley: Chichester, 1994.
- (2) Colthup, N. B.; Daly, L. H.; Wiberley, S. E. *Introduction to Infrared and Raman Spectroscopy*; Academic Press: New York, 1975.
- (3) Scheinmann, F. *An Introduction to Spectroscopic Methods for the Identification of Organic Compounds*; Pergamon Press: Oxford, 1970.
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- (5) Kozima et al. *J. Organomet. Chem.* **1975**, 92, 303, 305, 309.
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- (7) Dunciac, J. V.; Pierce, M. E.; Santella, J. B. *J. Org. Chem.* **1991**, 56, 2395–2400.
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- (9) Schering, A. G. *Organozinn-Verbindungen, Hinweise zur Toxikologie und sicheren Handhabung* **1985**, Bergkamen.
- (10) Attar, K. M. *Appl. Organomet. Chem.* **1996**, 10, 317–337.
- (11) Harrington, C. F.; Eigendorf, G. K.; Cullen, W. R. *Appl. Organomet. Chem.* **1996**, 10, 339–362.

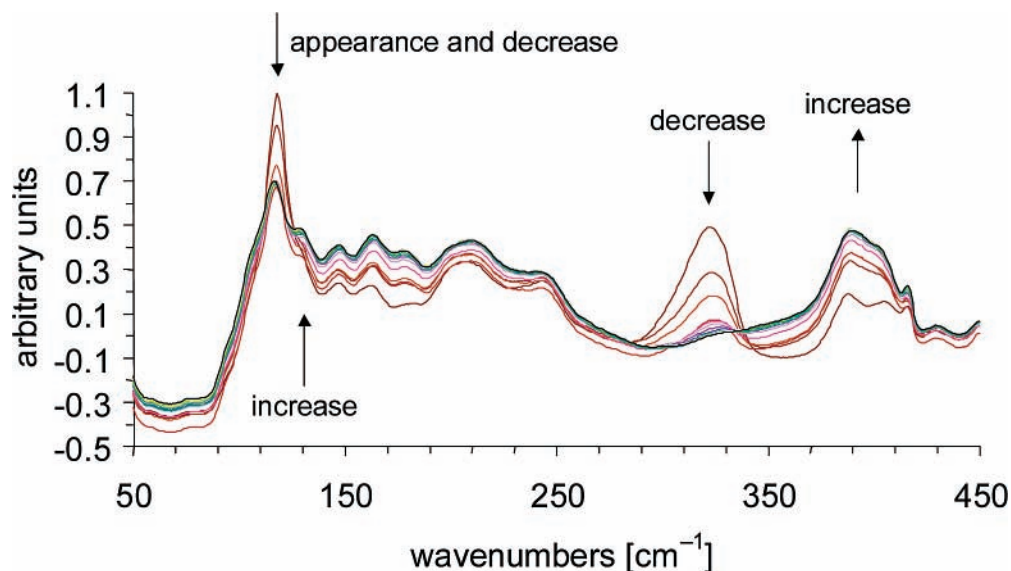


Figure 1. Raman spectra at intervals of 1 h; normalized data; spectral range: 50–450 cm^{-1} .

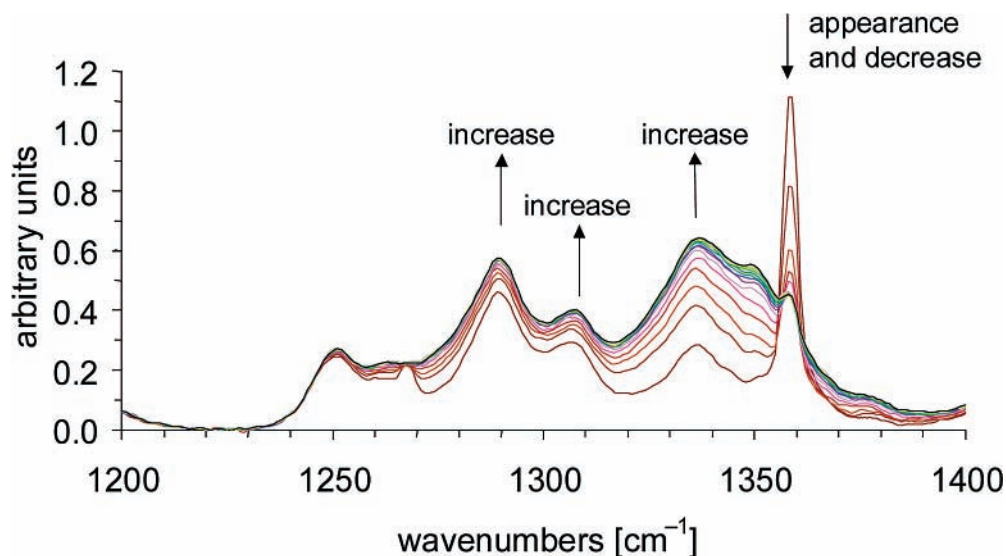


Figure 2. Raman spectra at intervals of 1 h; normalized data; spectral range: 1200–1400 cm^{-1} .

(i) appearance and decrease of peak at around 125 cm^{-1} (sole crystal lattice vibration of NaN_3 single crystals¹²): addition and conversion of NaN_3 .

(ii) decrease of peak at around 325 cm^{-1} ($\nu_{\text{Sn-Cl}}$ ¹³): conversion of Bu_3SnCl .

(iii) increase of peak at around 385 cm^{-1} : formation of Bu_3SnN_3 .

(iv) increases of several peaks between about 1240 and 1390 cm^{-1} (τCH_2 , ωCH_2 , and $\delta_s\text{CH}_3$): formation of $\text{Bu}_3\text{-SnN}_3$; changes in peak intensities probably due to changes in the dipole moments of the corresponding bonds.

(v) appearance and decrease of peak at around 1360 cm^{-1} ($\nu_s\text{N}_3$ in NaN_3): addition and conversion of NaN_3 .

(vi) appearance and increase of peak around 2065 cm^{-1} ($\nu_{\text{as}}\text{N}_3$ in Bu_3SnN_3 ; $\nu_s\text{N}_3$ in Bu_3SnN_3 is said to appear around 1290 cm^{-1} ,¹⁴ but was not observable as an isolated peak of significant intensity in our case): formation of Bu_3SnN_3 .

3.1.3.3. FTIR Data. The FTIR spectroscopic measurements were performed with an ATR diamond probe. With this technology, only solvents, liquids, and dissolved compounds can be observed. Thus, for the investigated chemical reaction, only the two liquid compounds, tri-butyltin chloride (Bu_3SnCl) and tri-butyltin azide (Bu_3SnN_3), could be detected.

The most important changes in the FTIR spectra are summarized below (see Figure 4):

(i) Appearance and increase of peak at around 1290 cm^{-1} ($\nu_s\text{N}_3$ in Bu_3SnN_3): formation of Bu_3SnN_3 .

(ii) Due to the strong absorption of diamond in the spectral domain between 2000 and 2500 cm^{-1} , the peak caused by the asymmetric stretching vibrations of N_3 in Bu_3SnN_3 cannot be observed.

(iii) As for the Raman data, the increase of several peaks between about 1240 and 1390 cm^{-1} was observed.

3.1.4. Conclusions. The concentration variations of the involved compounds were estimated directly from individual band intensities. Characteristic spectral bands could be

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(13) Geissler, H.; Kriegsmann, H. *J. Organomet. Chem.* **1968**, *11*, 85–95.

(14) Cheng, H. S.; Herber, R. H. *Inorg. Chem.* **1970**, *9*, 1686–1690.

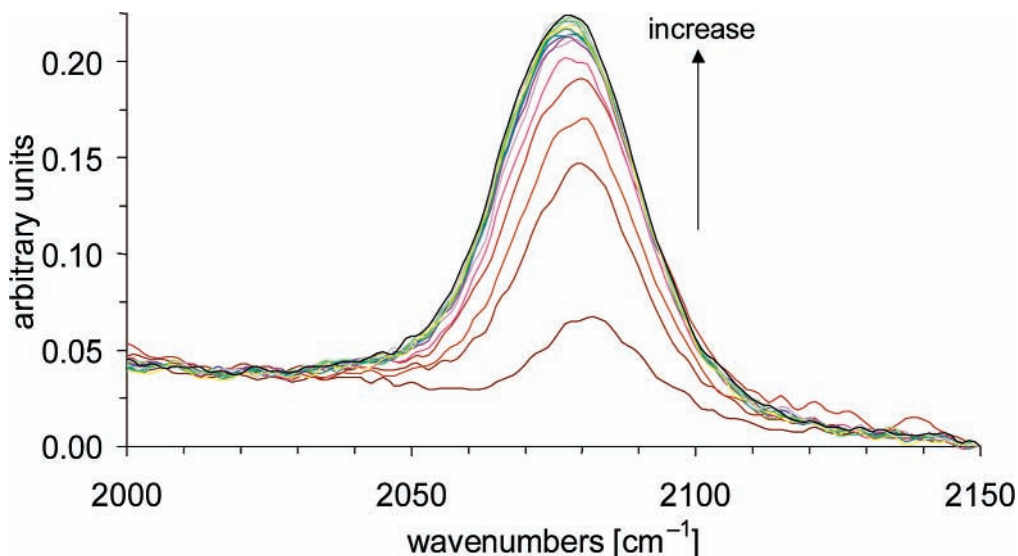


Figure 3. Raman spectra at intervals of 1 h; normalized data; spectral range: 2000–2150 cm^{-1} .

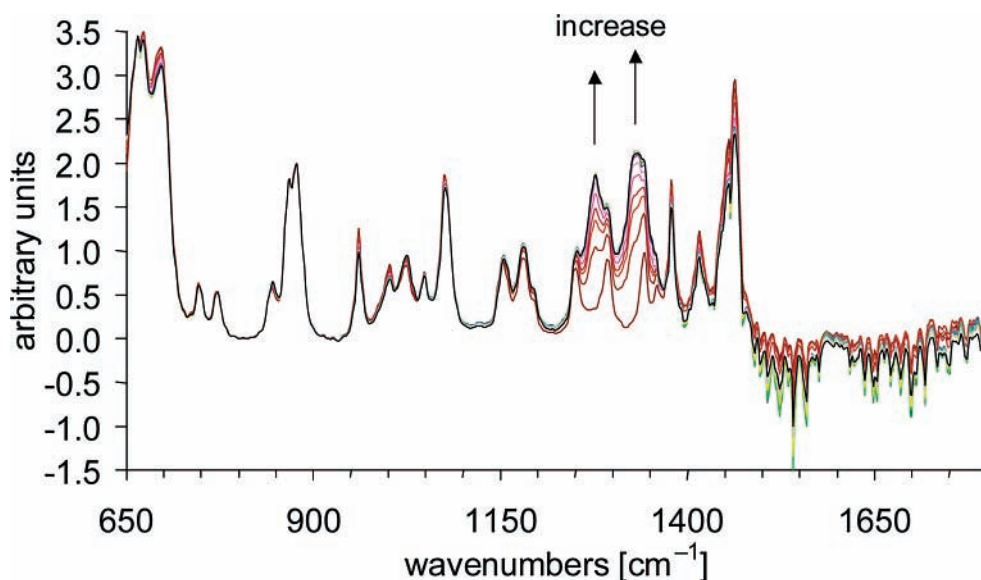


Figure 4. FTIR spectra at intervals of 1 h; normalized data; spectral range: 650–1800 cm^{-1} .

observed for all compounds using RAMAN spectroscopy (see Figure 5). With this method, both solid and liquid compounds can be observed. The spectra showed sharp, often isolated peaks (typical for Raman spectroscopy).

FTIR spectroscopy, however, only allowed the observation of the formation of tri-*n*-butyltin azide. Due to the utilization of an ATR probe, only liquids and dissolved compounds could be observed. The conversion of Bu_3SnCl cannot be seen (the peak corresponding to $\nu\text{Sn}-\text{Cl}$ is located outside of the spectral range of our FTIR instrument). The spectra show broader peaks, resulting in a more difficult data analysis. Nevertheless, the corresponding reaction profiles for the formation of tri-*n*-butyltin azide agreed well with those obtained from the RAMAN data (see Figure 6).

The end point of the reaction can be determined qualitatively as the point from which the intensity of the product peaks remains constant within the limits given by the noise of the methods.

3.2. Synthesis of 2-Chloroaniline. 3.2.1. Introduction.

Reduction of nitro compounds to amines is an essential step

in what is probably one of the most important synthetic routes in aromatic chemistry. Nitro compounds are readily prepared by direct nitration; when a mixture of *o*- and *p*-isomers is obtained, it can generally be separated to yield the pure isomers. The primary aromatic amines obtained by the reduction of these nitro compounds are readily converted to diazonium salts; the diazonium group, in turn, can be replaced by a large number of other groups. In many cases this sequence is the best method of introducing these other groups into the aromatic ring. In addition, diazonium salts can be used to prepare an extremely important class of compounds, the azo dyes.

The catalytic hydrogenation of aromatic nitro compounds is a class of reaction with a high hazard potential. Nevertheless, a large variety of different aromatic nitro compounds are reduced to amines in the fine chemical industry. The hazards of such reactions are the following:¹⁵

(15) Stoessel, F. J. *Loss Prev. Process Ind.* **1993**, *6*, 79–85.

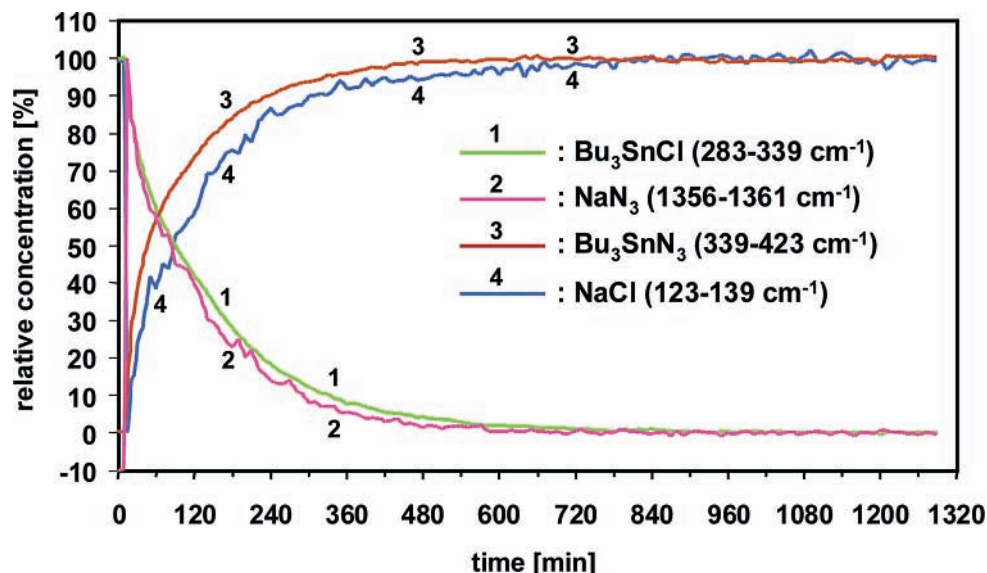


Figure 5. Normalized reaction profiles (maximum change in peak area set to 100%).

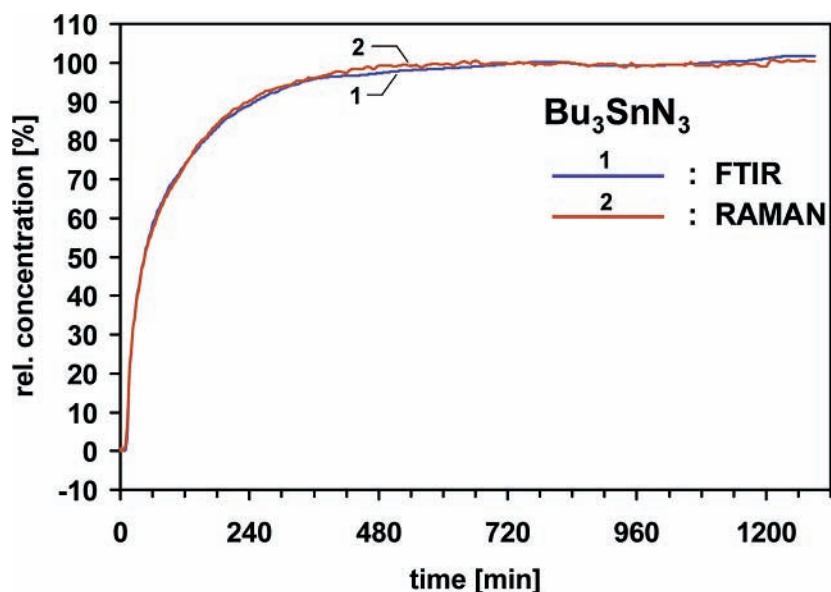


Figure 6. Variation of the relative concentration of Bu₃SnN₃ measured by FTIR and Raman.

(i) hazards related to hydrogen (explosive hydrogen/air mixtures, very low ignition energy),

(ii) hazards related to the catalyst (handling of pyrophoric substances, e.g. Raney nickel or platinum on carbon or palladium on carbon),

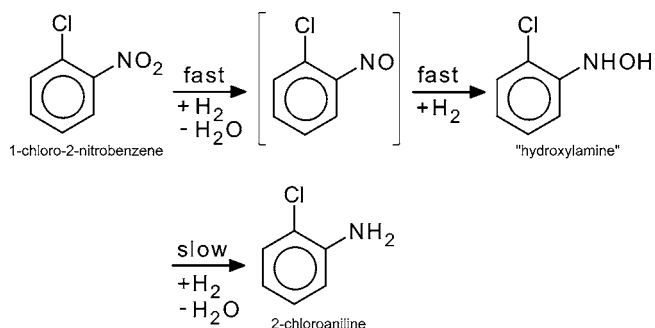
(iii) hazards related to the high decomposition energy of aromatic nitro compounds,

(iv) hazards related to the hydrogenation reaction (very exothermic reaction; in the case of a cooling failure, the decomposition of the aromatic nitro compound could be easily triggered), and

(v) hazards related to unstable intermediates (the accumulation of intermediate products as *N*-phenylhydroxylamine can lead to uncontrolled decomposition reactions).

This last point was specially investigated during this work. Indeed, all hazards concerning the high heats of reaction and decomposition can easily be determined and quantified using classical calorimetric methods. Another point was the utiliza-

Scheme 2. Synthesis of 2-chloroaniline



tion of spectroscopic methods to study heterogeneous catalytic reactions.^{16,17}

The chemical mechanism^{18,19} of the investigated reaction is described in Scheme 2.

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(17) LeBlond, C.; Wang, J.; Larsen, R.; Orella, C.; Sun, Y.-K. *Top. Catal.* **1998**, *5*, 149–158.

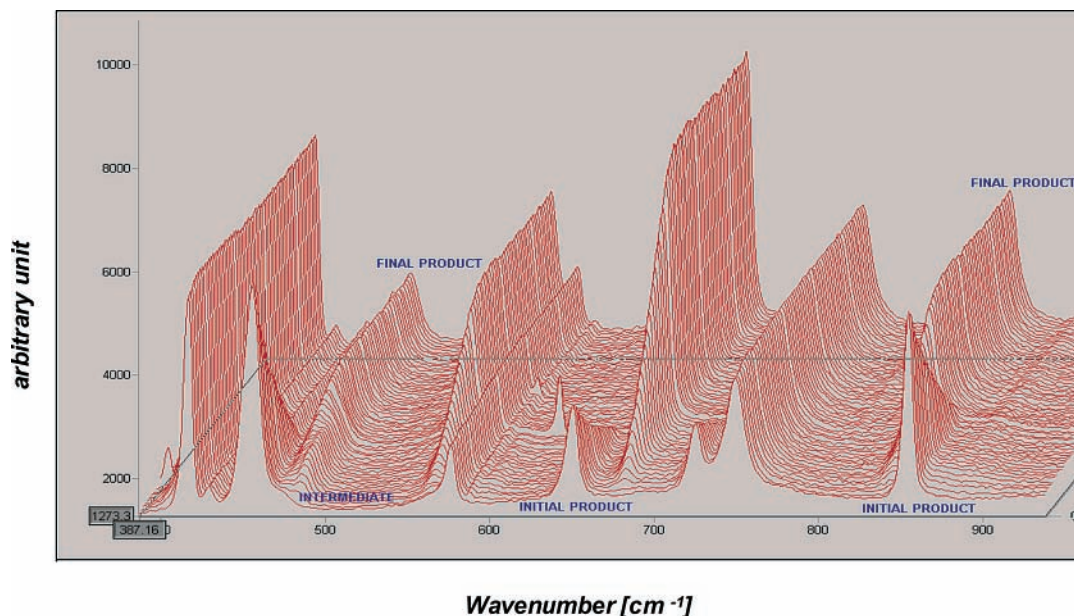


Figure 7. Raman spectra of the hydrogenation (385–920 cm^{-1}).

The overall reaction proceeds via nitroso and hydroxylamine intermediates, both of which are reactive and may undergo undesired condensation or disproportion reactions.²⁰ These reactions are not controlled by the hydrogen mass transfer and therefore cannot be stopped by reducing the agitation. Incidents due to the accumulation of *N*-phenylhydroxylamine are reported in the literature. A possible cause of such accidents is a contamination of the nitro compound that slows the last reaction step and therefore increases the proportion of *N*-phenylhydroxylamine.²¹ Therefore, the detection and the monitoring of unstable intermediates during the completion of the reaction are very important for the assessment of the process safety.

3.2.2. Experimental Section. 1-Chloro-2-nitrobenzene and methanol were charged at 20 °C in a stirred reactor (gassing propeller stirrer), and the reaction system was inerted with nitrogen. Then, Pt/C 5% [catalyst: platinum on carbon] was added, and a first calibration of the reaction calorimeter was performed. Then, the reactor was pressurized with hydrogen (1 bar), and the reaction mixture was stirred at the same temperature during 20 h. Finally, a repeat calibration was carried out.

3.2.3. Results and Discussion. 3.2.3.1. *Raman Data.* The most important changes in the Raman spectra are summarized below (see Figures 7 and 8):

(i) For the initial compound (1-chloro-2-nitrobenzene): the following bands are due to deformations of the $-\text{NO}_2$ group:

- (a) decrease of peak at around 455 cm^{-1} ,
- (b) decrease of peak at around 650 cm^{-1} , and
- (c) decrease of peak at around 850 cm^{-1} .

(ii) For the intermediate compound (*N*-phenylhydroxylamine): the following band is due to deformations in the $-\text{NH}-\text{OH}$ group:

(a) appearance of a weak band followed by its decrease at around 480 cm^{-1} .

(iii) For the final product (2-chloroaniline) the following bands are due to deformations in the $-\text{NH}_2$ group:

- (a) appearance and increase of peak at around 470 cm^{-1} ,
- (b) appearance and increase of peak at around 660 cm^{-1} , and
- (c) appearance and increase of peak at around 820 cm^{-1} .

The concentration variations of the initial compound, of the hydroxylamine intermediate and of the final product can be estimated by using band intensities from Raman spectroscopy. These concentrations are shown in the Figure 9.

3.2.3.2. *FTIR Data.* The most important changes in the FTIR spectra are summarized below (see Figure 10):

(i) for the initial compound (1-chloro-2-nitrobenzene):

(a) decrease of peak at around 780 cm^{-1} : NO_2 out-of-plane wag^{22,23}

(b) decrease of peak at around 853 cm^{-1} : NO_2 scissors deformation;

(ii) for the intermediate compound (hydroxylamine):

(a) the appearance of a weak band followed by its decrease was observed at around 872 cm^{-1} ; this peak corresponds probably to the N–O stretching;

(iii) for the final product (2-chloroaniline):

(a) appearance and increase of peak at around 680 cm^{-1} : N–H out-of-plane bending,

(b) appearance and increase of peak at around 749 cm^{-1} : N–H wagging,

(c) appearance and increase of peak at around 930 cm^{-1} : N–H out-of-plane bending,

(d) appearance and increase of peak at around 1011 cm^{-1} : C–N stretching vibration,

(18) Freifeld, M. *Practical Catalytic Hydrogenation: Techniques and Application*; Wiley: Chichester, 1971.

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(20) MacNab, J. I. *Runaway Reactions* **1981**, Paper 3/S, 1–15.

(21) Tong, W. R.; Seagrave, R. L.; Wiederhorn, R. *Loss Prev.* **1977**, *11*, 71–75.

(22) Green, J. H. S.; Harrison, D. J. *Spectrochim. Acta* **1970**, Part 1, 26, 1925.

(23) Green, J. H. S.; Lauwers, H. A. *Spectrochim. Acta* **1971**, Part 1, 27, 817.

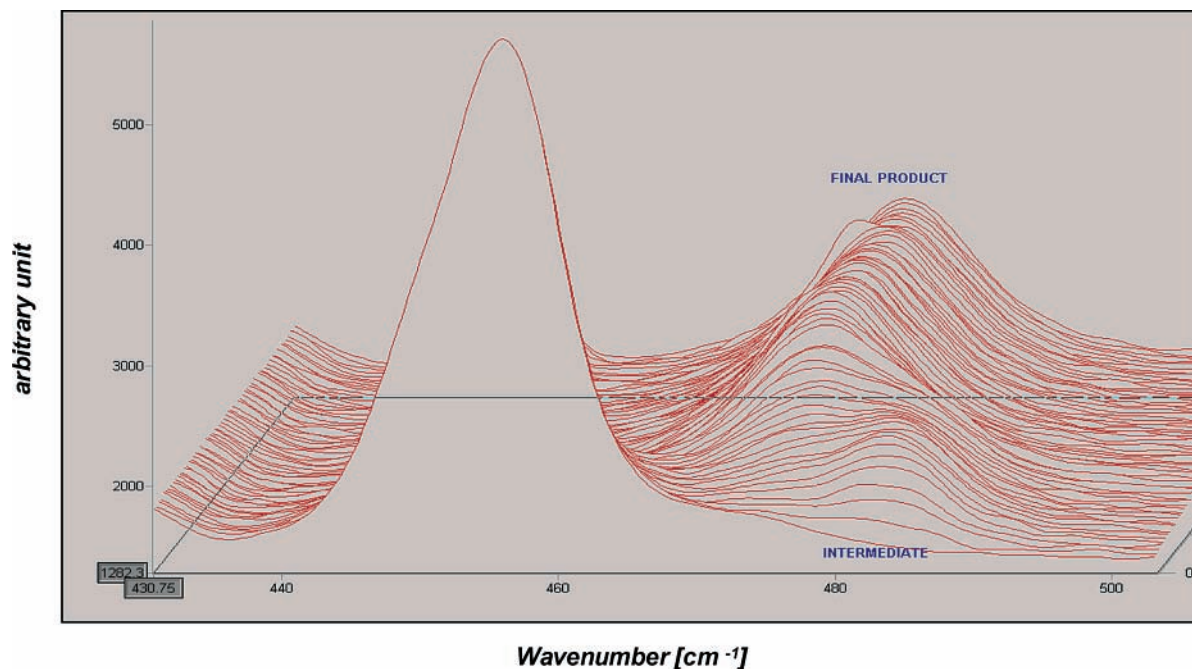


Figure 8. Raman spectra of the hydrogenation (430–500 cm^{-1}).

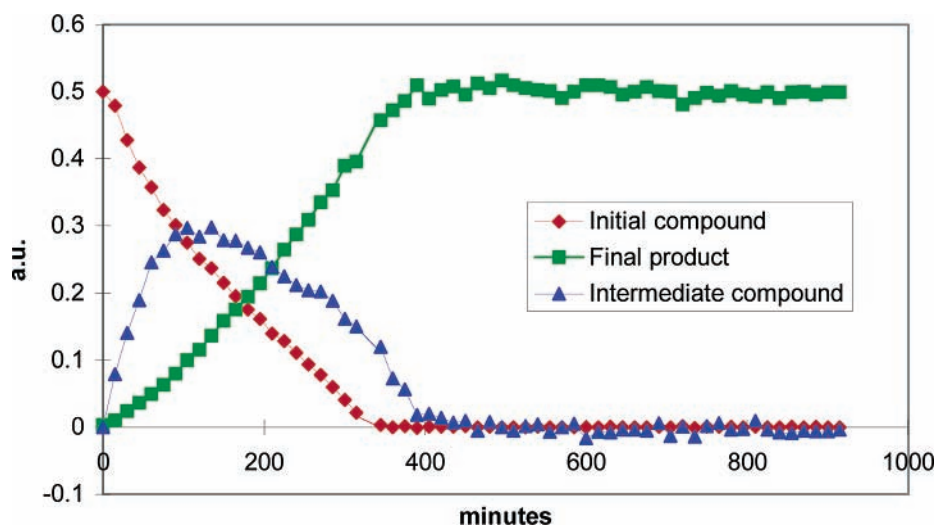


Figure 9. Normalized reaction profiles (Raman spectroscopy).

(e) appearance and increase of peak at around 2972 cm^{-1} : N–H stretching vibration.

The concentration variations of the initial compound, of the hydroxylamine intermediate and of the final product can be estimated by using FTIR spectroscopy. These concentrations are shown in the Figure 11.

3.2.4. Conclusions. Both methods are utilizable for the detection of the unstable *N*-phenylhydroxylamine intermediate. Under normal reaction conditions, the concentration of this compound is low (as during our study). Nevertheless, in case of process deviation, a higher concentration can occur due to the accumulation of this species. These spectroscopic methods are appropriate to monitor the reaction to ensure a safe completion of the chemical process.

4. Final Conclusions

Online spectroscopy is an important tool for the development and the monitoring of chemical processes. It allows

the detection of the formation and the accumulation of undesirable intermediates or side products, so as to determine the reaction end point, particularly when traditional analysis is only applicable with difficulty.

A fiber-optic connection between the probe and the spectrometer is more appropriate for industrial applications than bypass systems for sampling. With this technology, the spectrometer can be used in a pilot plant or a production plant without important modification of the available equipment. This device can be installed in a protected environment (e.g. in a control room for an explosion-safe installation). The online evaluation of the data and the process monitoring can be done with an expert system software.

Online spectroscopy can also be used for other applications, such as distillation operations, material identification (through-the-package analysis), catalysts analyses, and so forth. Undoubtedly, online spectroscopy will become a standard equipment in the chemical industry in the next years.

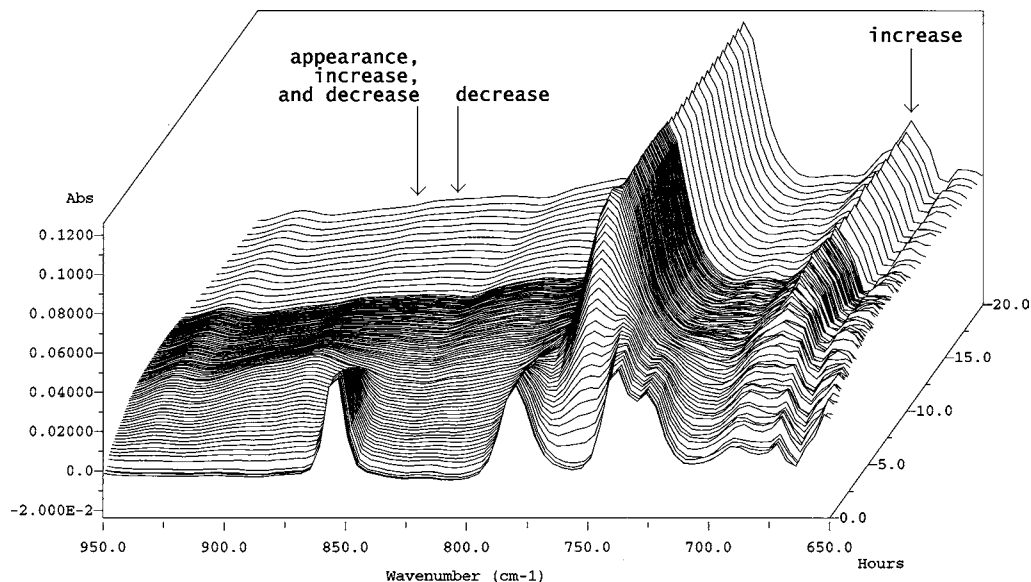


Figure 10. FTIR spectra of the hydrogenation (650–950 cm^{-1}).

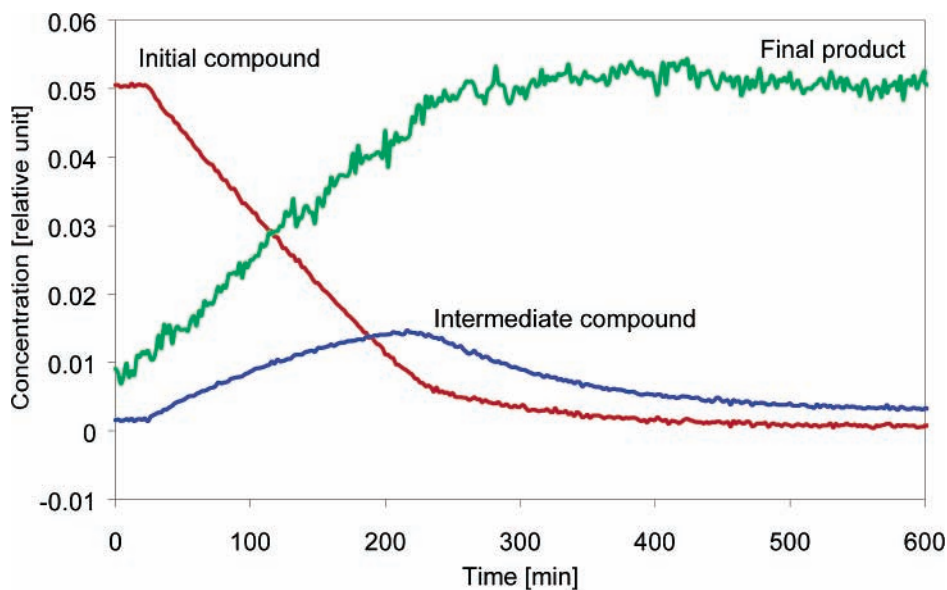


Figure 11. Normalized reaction profiles (FTIR spectroscopy).

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