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Use of Raman Spectroscopy to Characterize Hydrogenation Reactions

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Abstract:

Raman spectroscopy was used to characterize hydrogenation reactions involving single-step and two-step processes. The Raman technique was shown to be well-suited for endpoint determination as well as process optimization. In this investigation, hydrogenation of cyclohexene to produce cyclohexane was used as a model system. Conditions were varied to determine the effect of catalyst loading, solvent ratios, and reactant concentrations. Four catalysts were evaluated. The kinetic profiles of each reaction process were determined for each of the catalysts. In one case, a side reaction leading to an intermediate was observed for the hydrogenation reaction when run under hydrogen-starved conditions. After these cyclohexene hydrogenations were characterized, Raman spectroscopy was applied to the conversion of carvone to tetrahydrocarvone and the hydrogenation of 2-(4-hydroxyphenyl) propionate. Raman was used to characterize the kinetics of these reactions and was also used to prove that two-step hydrogenation mechanisms occurred in each. Raman was shown to be useful for process understanding, process optimization, process monitoring, and endpoint determination. Accomplishment of these goals leads to better process controls upon transfer of the procedure to a process environment. This ultimately leads, in turn, to the mitigation of risk of making out-of-specification product in manufacturing.

Introduction

Hydrogenation reactions are ubiquitous in chemical manufacturing processes. In the pharmaceutical industry, they are quite commonly used in multistep procedures employed in the synthesis of active pharmaceutical ingredients (APIs).[1] In fact, hydrogenation reactions account for about 10% to 20% of all reactions employed by API manufacturers.[1] This class of reactions is also used in the chemical industry for general synthetic procedures.

Hydrogenations can be performed to accomplish several types of chemical transformations, but they are often used to convert olefinic bonds to aliphatic bonds.[2] Other common conversions include transformation of nitro compounds to amines, functional group deprotection procedures, and other processes.[3,4]

With any synthetic reaction carried out on an industrial scale, it is useful to perform in-process checks in order to ascertain the progress of the reaction and know when the endpoint has been reached. In the case of hydrogenations, many of the reactions are inherently highly exothermic. Ineffective heat removal can result in thermal runaway leading to an explosion.[5] In these cases, monitoring of the progress of the reaction to avoid such events is essential. Real-time feedback through a monitoring scheme that allows for process adjustments is preferred.

In the pharmaceutical industry, active ingredient synthesis is often referred to as primary processing. The Process Analytical Technology (PAT) initiative proposed by the United States Food and Drug Administration (USFDA) has produced much activity in the realm of process chemistry amongst pharmaceutical companies.[6] The premise of this is that better understanding necessarily leads to the ability to impose better controls. In turn, a better control regime mitigates the risk of making product that is out-of-specification. Such a result provides benefits for both the consumer and the manufacturer. In the case of the manufacturer, benefits are realized by a reduction of scrapped materials and wasted production capacity as well as the reduction or elimination of costly product recalls. For the consumer, the benefit is the assurance that the product they use was manufactured to the highest standards for purity, safety, and efficacy as the processes are monitored in real time.

Vibrational spectroscopic techniques such as Fourier transform infrared (FT-IR) spectroscopy, near-infrared (NIR) spectroscopy and Raman spectroscopy are extremely valuable tools for many process situations. Various groups have experimented with NIR in the area of reaction monitoring. For example, hydrogenation of itaconic to methyl succinic acid was carried out by Wood et al.[7] Fermentation was monitored by Lendl et al.[8] Pharmaceutical companies have

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[†] Department of Pharmaceutics, University of Mississippi.

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(1) Pavlenko, N. V.; Tripolskii, A. I. L. V. *Res. Chem. Kinetics* **1995**, 207−258.

(2) Dyson, P. J.; Zhao, D. Hydrogenation. *Multiphase Homogeneous Catalysis* **2005**, *2*, 494−511.

(3) An Leeuwen, P. W. N. M.; Van Koten, G. *Catalysis* **1993**, *79*, 199−248.

(4) Jacobson, S. E. Catalytic hydrogenolysis of organic thiocyanates and disulfides to thiols. PCT Int. Appl. 1997, 17 pp.

(5) Rylander P. N. *Catalysts, Reactors, and Reaction Parameters. Hydrogenation methods*; Academic Press: Orlando, FL, 1985.

(6) Guidance for Industry PAT −A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. Center for Drug Evaluation and Research, Division of Food and Drug Administration. 2003

(7) Wood, J.; Turner, P. *Appl. Spectrosc*. **2003**, *57* (3), 293−8.

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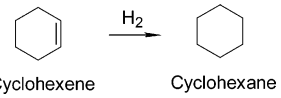
been actively working on using NIR to monitor syntheses[9] and also reaction completion in a closed loop hydrogenator.[10] In relation to NIR, Raman spectroscopy is fairly new to the area of reaction monitoring and particularly a convenient tool for real time process analysis.[11,12] Because Raman spectrometers such as NIR can be coupled to fiber optics, in situ sampling is possible. Raman is suitable for process monitoring for many reasons but chiefly because remote analysis is possible. Researchers have implemented this technology to monitor chemical reactions[13] as well as the synthesis[14,15] of compounds. Some more successful applications for the use of Raman in process analyses have been reported in the literature.[16−20]

For hydrogenation processes, Raman spectroscopy can be a very valuable tool to characterize kinetics and endpoints. This is especially true for conversion of olefins because Raman is very sensitive to the C═C double bond stretching.[21] Often such reactions can be followed by monitoring the disappearance of this band in the 1560−1680 cm^{-1} shift region. Raman spectroscopy has historically been applied for many applications involving olefins. It has been demonstrated as the preferred spectroscopic method for studying the microstructure of C═C bonds in polybutadiene.[22] In addition, the technique has been demonstrated as a means for monitoring the hydrogenation of polybutadiene using a number of catalysts.[23]

For processes involving olefins, regions other than the C═C stretch can also be monitored depending on the situation. In some cases, however, distinct bands are difficult to find. This is especially true when more than one species are involved in the reaction dynamics, such as the case when intermediates are produced that are Raman active. In such cases, curve deconvolution techniques such as Multivariate Curve Resolution (MCR) can be valuable for the successful extraction of significant information from Raman data.[24−26] This approach begins by generating initial estimates of spectral and corresponding intensity profiles by matrix decomposition methods. These initial estimates are neither physically meaningful nor typically the pure spectra of the components present in the sample. However, they can be transformed into physically meaningful solutions that represent the spectra of pure components by self-modeling methods.[26] The ability of factor analysis to reduce and resolve data matrices of chemical mixtures into pure component spectra and individual concentration profiles has been accomplished in several cases. These mixture analyses provide an estimation of the number of chemical species present, the identification of these species, and the determination of their concentrations. A very successful technique in analyzing vibrational spectroscopy data files is multivariate curve resolution (MCR), a group of techniques which intend the recovery of response profiles (spectra, pH profiles, time profiles, elution profiles) of the components in an unresolved mixture obtained in evolutionary processes when no prior information is available about the nature and composition of these mixtures.

The work described below represents an investigation of the capability of Raman spectroscopy to monitor hydrogenation reactions of interest to the pharmaceutical community. The utility of MCR as a data analysis tool was also demonstrated in this work. This study uses model compounds to highlight the potential benefits of Raman spectroscopy as an in situ PAT tool for the study of hydrogenations, which is an important class of industrial reactions.

Scheme 1. **Conversion of cyclohexene to cyclohexane**



Experimental Section

Materials. Platinum, 5 wt % on activated carbon, palladium, 5 wt % on carbon, rhodium, and Rainey Nickel were used for the hydrogenation reactions. These catalysts along with the reactants carvone, cyclohexane, and cyclohexene were obtained from Sigma-Aldrich Inc. (St. Louis, MO).

The compound 2-(4-hydroxyphenyl) propionate was prepared in the medicinal chemistry department at the University of Mississippi according to the published procedure.[27]

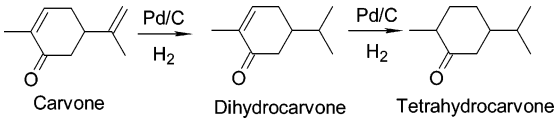
Hydrogenation Reactions and Products. Conversion of Cyclohexene to Cyclohexane. The first model system explored was that of the simple conversion of cyclohexene to cyclohexane (Scheme 1). Several catalysts were used for these reactions including palladium on carbon, platinum on carbon, rhodium complex, and Rainey nickel. A 100-mL three-necked flask was used for all reactions. The flask was covered with Al foil to avoid ambient light interference with the Raman scatter. One neck was stoppered with a serum

(8) Gunta, M.; Josef, D.; Josefa, R. B.; Erwin, R.; Bernhard, L. *Appl. Spectrosc.* **2004**, *58* (7), 804−810.
(9) Wiss, J.; Länzlinger, M.; Wermuth, M. *Org. Process Res. Dev.* **2005**, *9* (3), 365−371.
(10) Ward, H. W., II; Sekulic, S. S.; Wheeler, M. J.; Taber, G.; Urbanski, F. J.; Sistare, F. E.; Norris, T.; Aldridge, P. K. *Appl. Spectrosc.* **1998**, 52 (1), 17−21.
(11) Lewis, I. R. Process Raman Spectroscopy. In *Handbook of Raman Spectroscopy*; Lewis, I. R., Edwards, H. G. M., Eds.; Marcel Dekker: New York, 2001.
(12) Adar, F.; Geiger, R.; Noonan, J. *Appl. Spectrosc. Rev.* **1997**, *32*, 45−101.
(13) Fletcher, P. D.; Haswell, S. J.; Zhang, X. *Electrophoresis* **2003**, *24* (18), 3239−45.
(14) Lee, M.; Kim, H.; Rhee, H.; Choo, J. *Bull. Korean Chem. Soc.* **2003**, *24* (2), 205.
(15) Svensson, O.; Josefson, M.; Langkilde, F. W. *Eur. J. Pharm. Sci.* **2000**, *11* (2), 141−55.
(16) Gervasio, G. J.; Pelletier, M. J. AT-Process **1997**, *3*, 7−11.
(17) Lipp, E. D.; Grosse, R. L. *Appl. Spectrosc.* **1998**, *52*, 42−46.
(18) Al-Khanbashi, A.; Dhamdhere, M.; Hansen, M. *Appl. Spectrosc. Rev.* **1998**, 33, 115−131.
(19) Bauer, C.; Amram, B.; Agnely, M.; Charmot, D.; Sawatski, J.; Dupuy, D.; Huvenne, J.-P. *Appl. Spectrosc.* **2000**, *54*, 528−535.
(20) Wethman, R.; Ray, C.; Wasylyk, J. *Am. Pharm. Rev.* **2005**, *8* (6), 57−63.
(21) Linn-Vien, D.; Colthup, N. B.; Fateley, W. G.; Grasselli, J. G. *The Handbook of Infrared and Raman Characteristic Frequencies of Organic Molecules*; Academic Press: San Diego, 1991.
(22) Edwards, H. G. M.; Johnson, A. F.; Lewis, I. R.; McLeod, M. A. *Polymer* **1993**, *34*, 3184−3195.
(23) Frankland, J. A.; Edwards, H. G. M.; Johnson, A. F.; Lewis I. R.; Poshyadida, S. *Spetrochim. Acta, Part A* **1991**, *47*, 1511−1524.
(24) Budevska, B. O.; Sum, S. T.; Jones, T. *J. Appl. Spectrosc.* **2003**, *57* (2), 124−131.
(25) Tauler, R.; Smilde, A. K.; Henshaw, J. M.; Burgess, L. W.; Kowalski, B. R. *Anal. Chem.* **1994**, *66*, 3331−3344.
(26) Schoonover, J. R.; Zhang, S. L.; Johnston, C. T. *J. Raman Spectrosc.* **2003**, *34*, 404−412.
(27) Chin, C. S.; Lee, B.; Moo, J.; Song, J.; Park, Y. *Bull. Korean Chem. Soc.* **1995**, *16* (6), 528−33.

Table 1. **Conditions used for cyclohexene reactions**

	amounts		
entry	catalyst (% w/w)	cyclohexene (M)	methanol (mL)
1	Pd/C 12	0.48	20
2	Pd/C 8	0.48	30
3	Pd/C 7	0.49	30
4	Pd/C 8	0.48	30
5	Pt/C 12	0.48	20
6	Pt/C 12	0.58	20
7	Pt/C 8	0.58	25
8	Pt/C 7.75	0.48	30
9	Rd/C 12	0.48	20
10	Rd/C 8	0.71	20
11	Rd/C 6.7	0.48	30

Scheme 2. **Conversion of carvone to dihydrocarvone to tetrahydrocarvone**



cap, and the immersion probe was fitted through the cap into the reaction flask. The other two necks were closed with serum caps. In general, the system was charged with 0.1 g of the catalyst and 20 mL of methanol as the solvent. The system was initially evacuated and then filled with hydrogen using a balloon. The mixture was stirred magnetically making sure the catalyst was suspended in methanol and not clumped to one of the sides of the flask. 0.82 g of cyclohexene was added after 5 min. The solution was mixed using a magnetic stir bar. Hydrogen was added continuously to the system from the balloon throughout the course of the reaction. The reactions were started at ambient temperature and pressure. The pressure inside was maintained from the balloon. Spectral data were acquired in 3-min intervals using 200 exposures and 1 accumulation.

The effect of catalyst and solvent on the reaction rates and the rate constants were also examined. Table 1 indicates the concentrations of the catalyst, cyclohexene, and the amount of methanol used in the reactions.

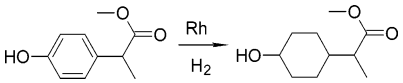
Reduction of Carvone to Tetrahydrocarvone. The applicability of Raman monitoring to the reduction of carvone (Scheme 2) was investigated. 21% w/w of the catalyst (Pd/C) was taken in 20 mL of the solvent (methanol). 1.5 g of carvone was added to the above mixture. The reaction setup used was similar to that used for the cyclohexene hydrogenations. Different conditions were also used like varying the amounts of catalyst, methanol, and carvone. Table 2 indicates the concentrations of each of these used in the reactions.

Reduction of 2-(4-Hydroxyphenyl) Propionate. The reduction of 2-(4-hydroxyphenyl) propionate (Scheme 3) was also studied using in situ Raman spectroscopy. 10 mmol (1.802 g) of the reactant was dissolved in methanol (25 mL). 5 mol % of Rhodium black (51 mg) catalyst was added. The reaction setup used was similar to that used for the cyclohexene and carvone hydrogenations.

Table 2. **Conditions used for carvone reactions**

	amounts		
entry	catalyst (Pd/C) (% w/w)	carvone (mmol)	methanol (mL)
1	3.5	20	30
2	7	10	30
3	21	10	20
4	5	10	30

Scheme 3. **Hydrogenation of 2-(4-hydroxyphenyl) propionate**



Raman Instrumentation and Data Analysis. Raman measurements were accomplished using a *RamanRxn1* dispersive Raman analyzer (Kaiser Optical Systems, Inc., Ann Arbor, MI). The instrument was equipped with either an Mk II or an MR Probe fiber optic probe head fitted with a short focal length immersion optic for sampling. The immersion optic was either 6 in. long with a $^1/_4$-in. diameter or 12 in. long with a $^1/_2$-in. diameter. The immersion optic was inserted directly into the reaction vessel for real-time monitoring. A 785-nm laser with 110 mW of power at the sample was employed for excitation. Spectra were collected using 60-s exposures over a spectral range from 150 to 3450 cm^{-1} at a spectral resolution of approximately 4 cm^{-1}.

HoloReact software (Kaiser Optical Systems) was used for data analysis, and Excel (Microsoft Corp., Redmond, WA) was used for simple curve fitting for kinetic models. Grams software (Thermo Electron, Salem, NH) was used for some data plots and manipulation. Data pretreatments included combinations of baseline correction using Pearson's method,[28] peak normalization, and/or window clipping. For the cyclohexene conversions, a simple area-under-the-curve measurement was used for trend plotting. The peak at 802 cm^{-1} was used to determine cyclohexane appearance, and the band at 823 cm^{-1} was used to follow cyclohexene disappearance. Quantitative conversions for kinetic modeling were based on the known starting concentrations of cyclohexene in each case.

A multivariate curve resolution[24−26] routine was applied to all of the cyclohexene reaction data. The reaction data were assessed for the formation of intermediate species. In the carvone and 2-(4-hydroxyphenyl) propionate reductions, MCR was used as the primary analysis technique due to the expected complexity of the reaction.

Results and Discussion

Cyclohexene Hydrogenations. The conversion of cyclohexene to cyclohexane was used as a model to confirm the potential use of Raman to monitor hydrogenation reactions under a variety of conditions. Figure 1 displays the spectral data for various time points in the process of one of the hydrogenation reactions. The region around the bands of interest between 650 and 950 cm^{-1} are highlighted.

(28) Pearson, G. A. *J. Magn. Reson*. **1997**, 27, 265.

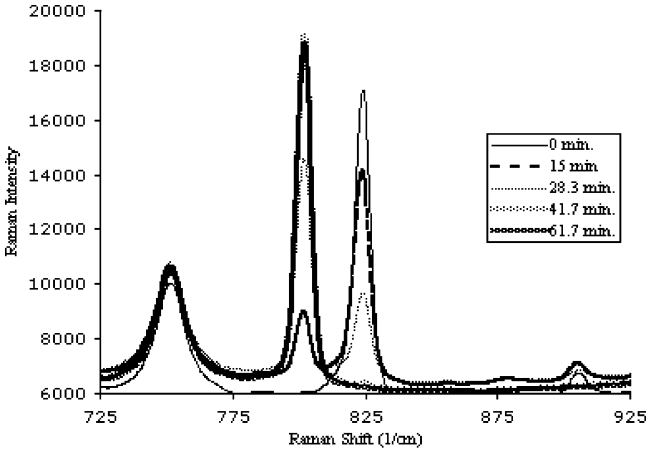


Figure 1. **Raman spectra extracted from the process of cyclohexene reduction to cyclohexane.**

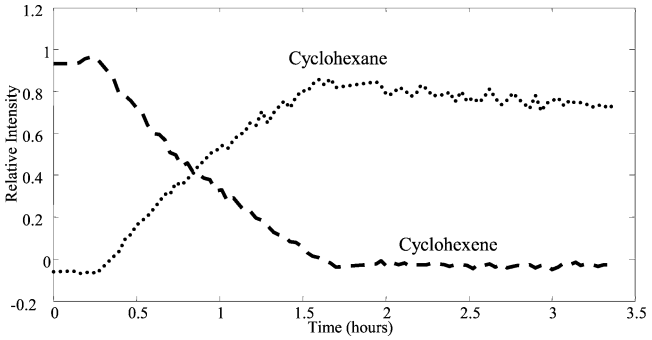


Figure 2. **Kinetic profile for the disappearance of cyclohexene with Pd/C as the catalyst.**

The resolved band for cyclohexane at 802 cm^{-1} clearly increases with time, while the resolved band for cyclohexene at 823 cm^{-1} clearly decreases with time. The band at 802 cm^{-1} corresponds to the CH_2 deformation plus ring breathing vibration of cyclohexane, and the one at 823 cm^{-1} corresponds to a similar vibrational mode of cyclohexene.

The trend of cyclohexene disappearance and cyclohexane formation can easily be followed qualitatively using the areas under the curves of the unique peaks previously noted (Figure 2). The advantage of using a band area ratio method for two unique peaks is that any baseline fluctuation will be effectively accounted for in the analysis. In the example shown, the reaction is completed between 1.5 and 2 h. It is noteworthy that if endpoint determination is all that is desired, this simple analysis is sufficient. Based on the initial concentration of cyclohexene, the intensity of the 802 cm^{-1} band was used to construct a quantitative model for the kinetic calculations.

Examples of the plots describing the kinetics of the cyclohexene reduction in the presence of Rh, Pt/C, and Pd/C can be viewed in Figure 3. Zero-order models provided the best fit for each set of reaction data. This is not unusual for hydrogenation reactions.[29] Cyclohexene reactions in the presence of Rh, Pt/C, and Pd/C gave rate constants of 0.310, 0.504, and 0.842 mol L^{-1} h^{-1}. The cyclohexene reactions were run in duplicate with each of the catalysts. From the data, it appears that Pd/C and Pt/C were similar in promoting efficient reactions and were superior to Rh in this regard.

(29) Paseka, I. *J. Catal.* **1990**, *121*, 349−55.

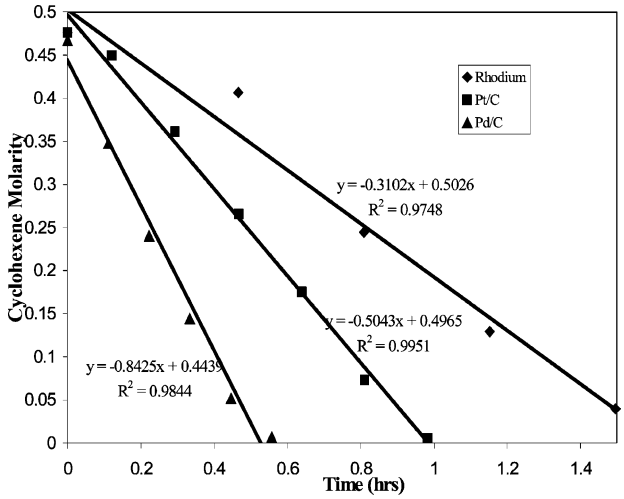


Figure 3. **Kinetics of cyclohexene in the presence of rhodium, Pt/C, and Pd/C.**

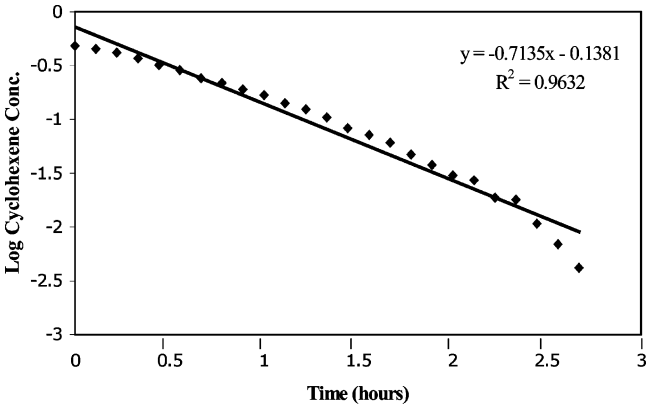


Figure 4. **First-order kinetics of cyclohexene with Rainey Nickel as the catalyst.**

In the cyclohexane reaction, Raman spectroscopy provided information to allow the choice of optimal catalyst. Rainey Nickel was also employed as a catalyst for this reaction. However, the mechanism using this catalyst is proposed to be different, as a first-order plot shown in Figure 4 appeared to model the data better than a zero-order plot. This suggests that the reaction in the presence of Rainey Ni was different from the other three.

Another aspect of analytical data collection during process development is the ability to understand processes better. This leads to the ability to better control processes in production. In one case using Pd/C as a catalyst, it was noted that there was a 15 to 20 minute delay before cyclohexane began to appear and cyclohexene began to disappear suggesting a significant reaction induction period.

This case was investigated further using MCR data analysis. Data were pretreated using a baseline correction according to Pearson's method. A four-factor analysis indicated that an unanticipated side reaction might have occurred during the induction delay. The MCR results are shown in Figure 5. The first trend profile is consistent with cyclohexane formation (with the allowance for solid clumping on the optic), and the plot of the factor "spectrum" is similar to the cyclohexane spectrum. Catalyst clumping on the window of the optic can be a common problem with

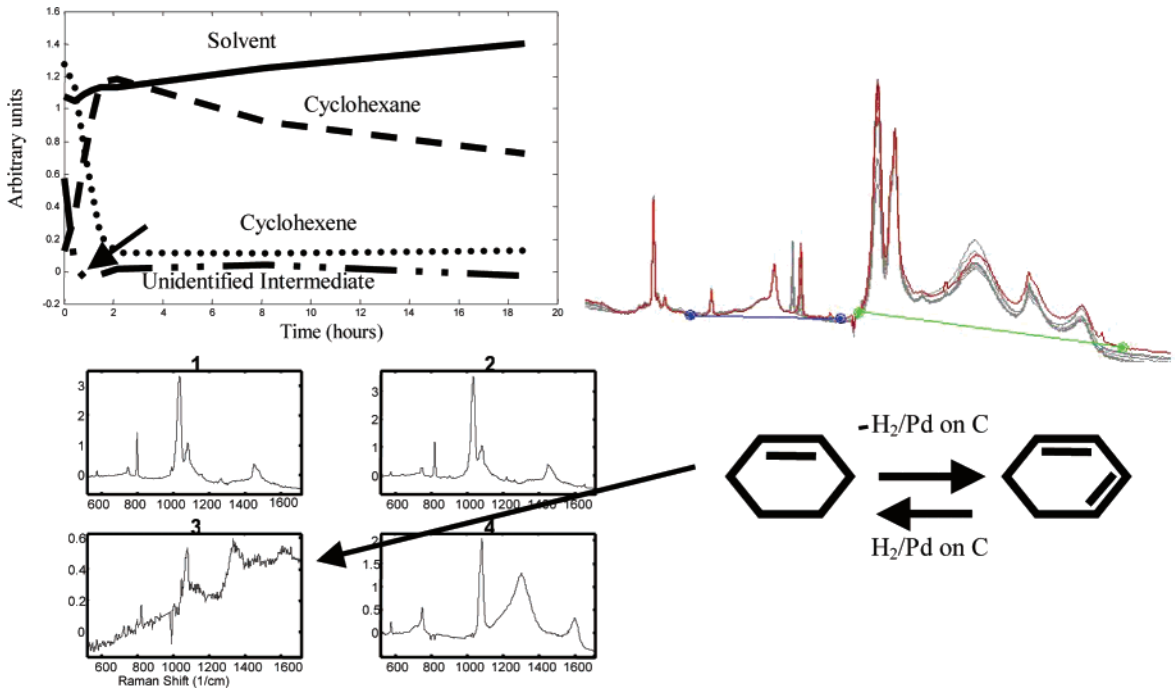


Figure 5. **MCR data analysis for Raman spectra for the cyclohexene reduction using Pd/C as the catalyst.**

heterogeneous catalysts and points out the importance of the positioning of the probe relative to the stir bar. This mostly occurred when the magnetic stir bar was not in the center forming a small vortex. This caused the peak intensities to go down due to obscuration of the probe window by the catalyst. This was evident from the particle aggregation on the optic. Care was taken to cover the hole drilled in the serum cap for inserting the probe.

The second MCR factor data are similar to the spectral features of cyclohexene, and therefore the second profile can be assigned to the disappearance of cyclohexene. The fourth profile remains relatively constant throughout the reaction (with allowance for solid clumping on the probe that affected overall Raman intensity) and is attributed to the methanol solvent. The third trend plot is of greatest interest. This profile begins at a finite level and then begins to disappear immediately. This transient material seems to be completely depleted in 30 to 45 min. This roughly corresponds to the induction time found in the simple area-under-the curve plots (Figure 2) for this reaction. The factor plot in this case is quite noisy and, thus, indicates a low level of spectral variation responsible for the composition of the factor.

The presence of a factor that seems to complement the induction time suggests that it could represent real chemical information. Because of the noise inherent in the factor plot, it is difficult to establish an identity for this potential intermediate with complete certainty. The factor plot appears to contain some features that may be assigned to solvent peaks. However based on the most intense features observed in the MCR plot (peaks at 827, 1073, 1333, and 1593 cm^{-1}) and the general knowledge of the chemistry, we have postulated that this is a material related to a transient intermediate involving a cyclohexene−Pd complex. Such information can be gained in real time from the combination of Raman spectroscopy and MCR analysis. Such knowledge can prove to be invaluable, as it would have been extremely difficult to obtain this level of understanding in the absence of real-time chemical monitoring. In this experiment the intermediate was benign and did not represent a safety hazard. However the production of unstable intermediates is not uncommon during hydrogenations. The ability to observe, track, and generate kinetic information on the formation and concentration of intermediates is particularly valuable when designing and operating a production-scale reactor.

Not surprisingly, it was found that the kinetic profiles changed when the ratios of the solvent, catalyst, and reactant were altered. Any changes in these ratios caused a significant change in the overall kinetics of the reaction. For example, the reduction in Pd/C catalyst and reactant relative to overall solvent caused a significant decrease in the rate of reaction. This can be assigned to a simple dilution effect with a reduction in the availability of hydrogen at the catalyst site for hydrogenation. Another noteworthy observation was that the spectral signal seemed to decrease in magnitude if the reaction was allowed to proceed for a long time. This could be due to the catalyst physically adhering to the window of the immersion optic, as was observed in some cases when the probe was removed from the reaction vessel. This understanding is valuable to the process engineer responsible for implementing the on-line analyzer. In the design of the production implementation, catalyst adherence could be accounted for by employment of a solvent wash step, an agitator, better positioning of the optic face relative to the flow, etc.

Carvone Hydrogenation. The kinetic profile of the two-step reduction of carvone to tetrahydrocarvone is shown in Figure 6. This reaction[30] is known to proceed through a two-

(30) Coche, L.; Ehui, B.; Limosin, D.; Moutet, J. C. *J. Org. Chem.* **1990**, *55* (23), 5905−10.

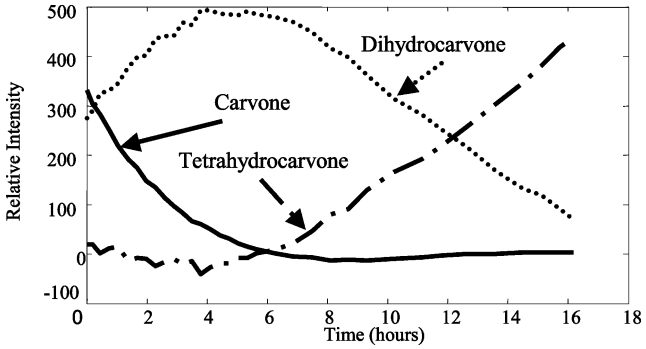


Figure 6. **MCR data analysis profiles for carvone reduction.**

step mechanism. Because the C═C bond endo to the ring is resonance stabilized with the carbonyl group, it is expected that the double bond exo to the ring will be hydrogenated selectively before the resonance-stabilized double bond. The reduction of carvone in the presence of various catalysts has been studied by several researchers.[31,32]

To monitor the reduction of carvone, the bands between the 452−498 cm^{-1} and 1134−1194 cm^{-1} shift were chosen. These regions were considered to account for the symmetric C−C═C stretch vibration which occurs in the region near 1130 cm^{-1}. The data were clipped, and a baseline correction using Pearson's method was performed. The data were then normalized to the band at 1082 cm^{-1} prior to MCR analysis. Three factors were generated using MCR.

The first profile shown in Figure 6 is consistent with a substance in solution at the beginning of the process. According to the profile, this material is consumed over the course of about 7−8 h. This represents the starting material carvone. A second profile is consistent with a substance that is absent until approximately 5−6 h after the start of the hydrogenation. This material then increases in level through about 16 h after the commencement of the reaction. This represents the ultimate product tetrahydrocarvone. The third profile represents the intermediate dihydrocarvone as it increases in level after the beginning of the hydrogenation peaking in concentration approximately 4 h into the reaction procedure. It then decreases through the remainder of the time that the process was monitored. The rate constant for carvone reduction in the presence of Pd/C as the catalyst was calculated to be 0.150 mol L^{-1} h^{-1} (Figure 7).

MCR analysis of the data leads to a three-factor result that is consistent with the proposed two-step reaction mechanism. The analysis clearly showed three profiles that are assigned to (a) the loss of carvone (the reactant), (b) the formation of dihydrocarvone (an intermediate), and (c) the subsequent formation of the required product (tetrahydrocarvone). The profiles suggest that tetrahydrocarvone is only formed by hydrogenation of the intermediate. The results are consistent with the literature[31] which suggests the existence of an intermediate as the reduction of carvone proceeds. The reduction of carvone to tetrahydrocarvone is very common unlike the reduction of carvone to dihydrocarvone, which is very selective. [30]

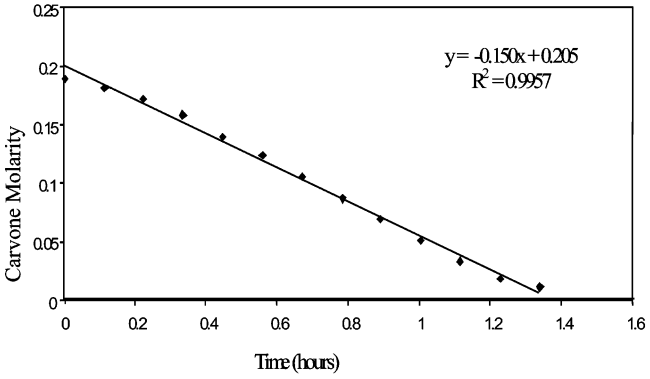


Figure 7. **Kinetics of carvone reduction.**

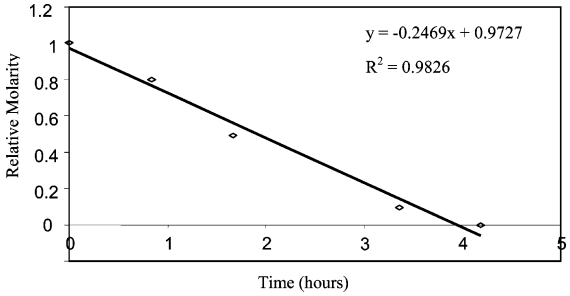


Figure 8. **Kinetic profile of 2-(4-hydroxyphenyl) propionate reduction.**

2-(4-Hydroxyphenyl) Propionate Hydrogenation. The kinetic profile for the reduction of 2-(4-hydroxyphenyl) propionate is shown in Figure 8. The MCR analysis was performed using the spectral region from 250 to 1700 cm^{-1}, and the resulting profiles (Figure 9) suggested the formation of an intermediate product, which was confirmed off-line by TLC. The intermediate detected is likely the compound with a partially hydrogenated ring. The initial hydrogenation step is the most difficult and can be accomplished only through the facilitation of the phenolic group.[33] This hydrogenation reaction is similar to the reduction of phenol to cyclohexanol, which has been looked at by Gonzalez-Velasco et al. and others.[34,35] This initial reduction phase likely produces the observed intermediate prior to more rapid reduction to the ultimate product. As can be seen from Figure 9, there appears to be a buildup of intermediate that is detectable. This seems accurate as the result is confirmed by TLC. This may suggest that the kinetics of the second step may not be as fast relative to the subsequent reduction as anticipated. The rate constant for the reduction of the propionic acid derivative was found to be 0.247 mol L^{-1} h^{-1}. Although the product can be detected, the profile for this material appears to be much noisier than the profiles for the reactant and intermediate because the product no longer has an aromatic functional group. This sort of conversion often will reduce the propensity for Raman scatter.

(31) De Miguel, S. R.; Roman-Martinez, M. C.; Cazorla-Amoros, D.; Jablonski, E. L.; Scelza, O. A. *Catalysis Today* **2001**, *66* (2−4), 289−295.
(32) Cerveny, L. Chemical Engineering Communications **1989**, *83*, 31−63.
(33) Griffin, K. G.; Hawker, S.; Johnson, P.; Palacios-Alcolado, M. L.; Calyton, C. L. *Chem. Ind. (Dekker)* **2003**, *89*, 529−35.
(34) Gonzalez-Velasco, J. R.; Gutierrez-Ortiz, J. I.; Gonzalez-Marcos, J. A.; Romero, A. *Reaction Kinetics and Catalysis Letters* **1986**, *32* (2), 505−12.
(35) Mahata, N.; Vishwanathan, V. *Journal of Molecular Catalysis A: Chemical* **1997**, *120* (1−3), 267−270.

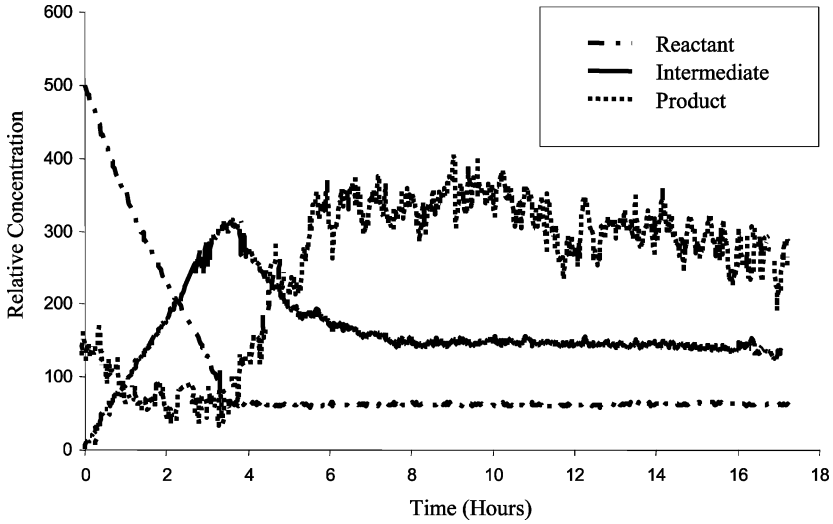


Figure 9. **Kinetic profile of 2-(4-hydroxyphenyl) propionate reduction suggesting the detection of an intermediate.**

This process was the most complex among the reactions investigated and represents a case in which process understanding is critical before scale-up. Understanding the conditions under which the production of the intermediate occurs and the kinetics and thermodynamics of the overall process are critical to successful transfer to a production environment. Raman spectroscopy was demonstrated to help with this critical level of understanding.

Conclusions

In this work, the use of Raman spectroscopy as an analytical tool for monitoring hydrogenation processes has been demonstrated. The results of the Raman spectroscopic analyses led to increased reaction understanding for these processes. In one process, a side reaction was observed that would not have been detected without the use of in situ spectroscopic analysis. In two other reactions, analyses of the Raman spectra lead to the confirmation of the presence of reaction intermediates. In addition to the observation of intermediates, kinetic profiles of each reaction were also elucidated and, in the case of the cyclohexene reduction, the optimal catalyst was identified. The ability to observe and quickly identify intermediates in situ and in real time is very important to the industrial organic chemist. Elucidating reaction mechanisms can be crucial to safely scaling-up a new synthesis and can be important when controlling the overall process. In addition, Raman spectroscopy was demonstrated as a tool for reaction endpoint determination that, if utilized in production, would translate into efficient reactor usage, which is a quantifiable business benefit.

The knowledge gathered regarding the kinetics of the reactions led to further enhanced reaction understanding. This understanding could be used for process optimization to identify process excursions and allow for timely adjustments to maintain the desired outcome. These adjustments could include varying the reaction conditions such as temperature, stirring rate, reagent addition, or reaction time.

The results of this work suggest that a real-time in situ Raman spectroscopic tool is an attractive alternative to traditional off-line laboratory-based analytical techniques such as thin-layer chromatography (TLC), high-pressure liquid chromatography (HPLC), or nuclear magnetic resonance (NMR) spectroscopy. In comparison to these techniques, in situ Raman analysis offers the benefits of faster analysis time and faster feedback to the operator. It also facilitates averting the requirement to sample the process thus avoiding potential exposure of production workers to hazardous reagents, minimizing contamination, and avoiding sampling issues including nonrepresentative sampling.

In this work Raman spectroscopy has been demonstrated as a real-time, in situ tool for monitoring hydrogenation reactions. Hydrogenation reactions are an important class of reactions that are often employed during the complex multistage synthesis of active pharmaceutical ingredients. The understanding and ability to optimize stages within an active pharmaceutical substance's production may be considered under the umbrella of the US FDA's PAT initiative. The PAT initiatives goals include (1) increasing process understanding, (2) facilitating process monitoring, and (3) providing a mechanism for process optimization and control in order to guarantee the maintenance of product quality. Using analytical tools to understand processes during the development phase leads to the ability to design more robust processes that should result in a reduced risk of producing an out-of-specification product. In summary, using the hydrogenation of model compounds Raman spectroscopy has been demonstrated as a tool capable of meeting and accomplishing many of the PAT initiative's goals.

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