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Testing the Validity of Microwave-Interfaced, in Situ Raman Spectroscopy as a Tool for Kinetic Studies

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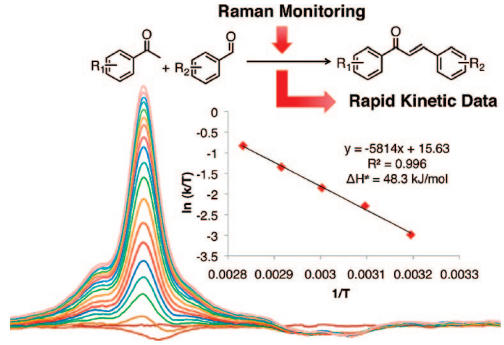
ABSTRACT



Raman spectroscopy in conjunction with microwave heating is a convenient and robust tool for monitoring organic reactions from a qualitative perspective. Its validity as a method for obtaining quantitative data is shown. Activation enthalpies for the synthesis of a range of substituted chalcones are determined and the results compared with well-established previous data and reactivity trends for this aldol condensation. The methodology is used for obtaining previously unreported pK_a data for substituted acetophenones.

Using microwave heating as a tool in organic chemistry has many advantages. Reactions are often complete in a matter of minutes and product yields can, in many cases, be improved.[1] A significant issue with performing reactions with microwave apparatus is that monitoring its progress generally requires stopping it, allowing the reaction mixture to cool and then using standard analysis techniques such as IR and NMR spectroscopy. Building on initial reports by Myrick et al.[2] and Pivonka and Empfield,[3] there has been a dedicated focus within our group to explore the scope and limitations of employing Raman spectroscopy to monitor microwave-promoted organic reactions from a qualitative perspective.[4,5] There are many aspects of Raman spectroscopy that make it well-suited to be an effective reaction monitoring tool. First, it relies on light scattering so there is no physical or mechanical interaction with the reaction sample. Next, although Raman signal strength is proportional to a number of variables including temperature, path length of the sample, laser intensity, and concentration, through the course of a reaction, all remain constant except concentration. This

(1) (a) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. (b) Loupy, A., Ed. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (c) Lidström, P.; Tierney, J. P., Eds. *Microwave-Assisted Organic Synthesis*; Blackwell: Oxford, UK, 2005.

(2) Stellman, C. M.; Aust, J. F.; Myrick, M. L. *Appl. Spectrosc.* **1995**, *3*, 392.

(3) Pivonka, D. E.; Empfield, J. R. *Appl. Spectrosc.* **2004**, *58*, 41.

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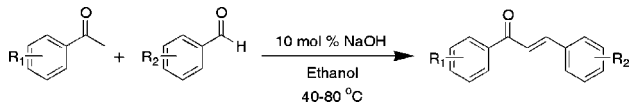
means that Raman spectroscopy is in theory an effective means to measure concentration changes in a dynamic system. Additionally, in terms of practicality, borosilicate glass is essentially transparent to a Raman spectrometer and this allows the use of standard laboratory glassware. Despite these advantages, while quantitative in situ infrared spectroscopy (e.g., ReactIR) has seen significant use for determination of reaction kinetics,[6] there are very few reports of analogous studies with Raman spectroscopy.[7] Recent advances in Raman spectroscopy now allow for data acquisition at such a rate that quantitative data can be extracted. In addition, microwave heating is also an ideal tool for performing kinetic studies since it offers reproducible, noncontact heating as well as precise temperature monitoring and data recording.[8] As a result we have become interested in using microwave-interfaced, in situ Raman spectroscopy for quantitative studies and have recently described a robust method to derive precise kinetic data for organic transformations.[9] In this letter we show further the validity of our methods for determing kinetic data by using established pK_a data as a standard to which to compare our results.

Scheme 1. Claisen−Schmidt Condensation



We chose to examine the Claisen−Schmidt condensation between an aromatic aldehyde and enolizable acetophenones (Scheme 1). The polarizable α,β-unsaturated ketone moiety of the chalcone system is highly Raman active and gives a characteristic signal at approximately 1600 cm^{-1}, thus allowing us to follow the reaction easily in real time (Figure 1).

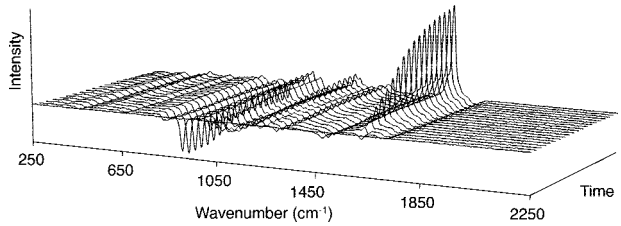


Figure 1. Typical three-dimensional Raman spectrum in the "fingerprint" region from 250 to 2250 cm^{-1} generated during the first 140 s of the Claisen−Schmidt condensation.

While the majority of microwave-promoted reactions are performed with use of sealed tubes, to perform quantitative work we use an open-vessel arrangement. Although this limits the temperature range to that from room temperature to the boiling points of solvents, the open-vessel format allows for a quantitative reaction start time as the catalyst is injected into the sample.

Starting with benzaldehyde and acetophenone as test substrates yielding *trans*-chalcone as product, our initial objective was to determine a calibration curve to transform units of Raman signal intensity to the standard kinetic parameters of concentration.[10] Since Raman signal strength when measuring only the Stokes shift is inversely proportional to temperature, it was necessary to derive calibration curves at each temperature the reaction would be monitored. This process was repeated for each chalcone product that would form part of our study.

We next turned our attention to monitoring the reactions. To ensure accurate and reproducible results, a stock solution of the appropriate benzaldehyde and acetophenone in ethanol was prepared from which 20 trials were performed. We ran four trials at each of five temperatures.[11] Raw spectral data were converted from units of Raman intensity•s^{-1} to standard units of rate (mol•L^{-1}•min^{-1}). With this kinetic data in hand, the Arrhenius plot of ln k vs $1/T$ was plotted for each reaction studied from which activation energies were calculated ($m = -E_a/R$, $R = 8.314$ J•M^{-1}•K^{-1}). Additionally, the Eyring plot of ln (k/T) vs $1/T$ was constructed for each reaction, from which the activation enthalpy, $\Delta H^{\ddagger}$, could be determined.[12] As an example, the condensation between acetophenone and benzaldehyde to yield chalcone was calculated to have an activation enthalpy of 49.0 kJ/mol (Figure 2), which is in good agreement for the previously reported value of 11.6 kcal/mol (48.5 kJ/mol).[13]

We calculated activation enthalpies for a wide range of substituted chalcones. After a few initial studies, we observed that the substitution on the acetophenone played a larger role in dictating the activation enthalpies than that on the aldehyde component. This is not unexpected since the rate-determining step of the reaction is proportional to the concentration of

(6) For selected recent examples see: (a) Denmark, S. E.; Pham, S. M.; Stavenger, R. A.; Su, X. P.; Wong, K. T.; Nishigaichi, Y. *J. Org. Chem.* **2006**, *71*, 3904. (b) Grabarnick, M.; Zamir, S. *Org. Proc. Res. Dev.* **2003**, *7*, 237. (c) Almeida, A. R.; Moulijn, J. A.; Mul, G. *J. Phys. Chem. C* **2008**, *112*, 1552. (d) Tibiletti, D.; Meunier, F. C.; Goguet, A.; Reid, D.; Burch, R.; Boaro, M.; Vicario, M.; Trovarelli, A. *J. Catal.* **2006**, *244*, 183.

(7) (a) Waal, D. D.; Heynes, A. M. *J. Solid State Chem.* **1989**, *80*, 170. (b) Ehly, M. E.; Gemperline, P. J.; Nordon, A.; Littlejohn, D.; Basford, J. K.; De Cecco, M. *Anal. Chim. Acta* **2007**, *595*, 80.

(8) For a recent kinetic study of a microwave-promoted reaction not involving in situ spectroscopy see: Gilday, J. P.; Lenden, P.; Moseley, J. D.; Cox, B. G. *J. Org. Chem.* **2008**, *73*, 3130.

(9) Schmink, J. R.; Holcomb, J. L.; Leadbeater, N. E. *Chem. Eur. J.* **2008**, *14*, 9943.

(10) To achieve this, solutions of known concentrations of *trans*-chalcone in ethanol were prepared. They were placed sequentially inside a round-bottomed flask inside the microwave cavity and brought to reflux by using microwave heating and then the Raman spectrum was collected. After subtraction of signals due to the solvent, a plot of signal intensity at 1598 cm^{-1} vs concentration was constructed.

(11) Stock solution (25 mL) was placed in a standard 50 mL capacity round-bottomed flask with a Teflon-coated stir bar, and this was placed into the microwave cavity. It was then heated to the desired temperature at which point a dark scan was taken. Next, the appropriate amount of sodium hydroxide catalyst in a small volume of water was injected and Raman spectra collected automatically at ~7 s intervals. The initial rate of reaction was determined by using the first few scans; generally under 1 min is all that is needed. As such, all 20 data points for a pair of substrates could be generated in a time period of less than 2 h.

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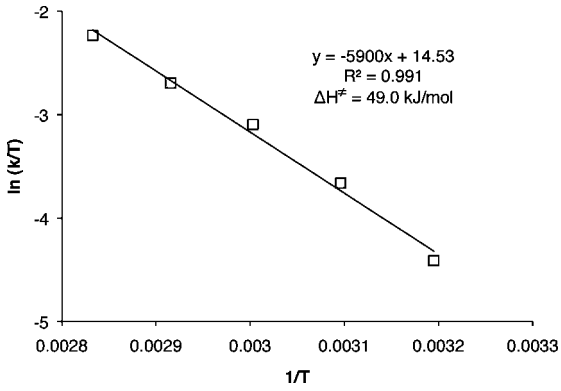

Figure 2. Typical Erying plot of ln(k/T) vs $1/T$ yielding a straight line, $y = mx + b$, $m = -\Delta H^{\ddagger}/R$, $\Delta H^{\ddagger} = 49.0$ kJ/mol, here for the formation of *trans*-chalcone. Each data point is the average of at least three trials agreeing to within 5%.

the enolate anion,[14] which in turn should be dependent upon the acidity of the α-proton of the substituted acetopheone. Since our kinetic data are extracted from the first few seconds of the reaction, three assumptions can be made: (1) [aldehyde] ≫ [enolate], (2) δ[aldehyde] ≈ 0, and (3) [chalcone] ≈ 0. This last point is especially important, as the retro-aldol reaction (regenerating starting materials) is in equilibrium with the forward reaction. Previous studies in which kinetic data were aquired over longer periods of time state that the substitution of the acetophenone has no impact on the activation energies for the reaction.[14] In stark contrast, we hypothesized that holding the aldehyde component constant in the reaction while varying the ketone substrate would show a strong correlation between activation enthalpies and pK_a values for the various acetophenones.

A plot of known pK_a values[15] for seven acetophenones (Table 1, entries 1, 2, 6, 7, 9, 10, and 14) vs our calculated activation enthalpies for their respective condensations with benzaldehyde (Figure 3) shows a strong correlation ($R^2 = 0.985$). We reasoned that we should be able to calculate, with reasonable certainty, pK_a data for additional acetophenones. For this study, we used both electron-rich and -poor ring systems as well as either mono-, di-, or tetrasubstituted acetophenones to explore more esoteric substitution patterns. We have determined for the first time the pK_a data for 2′-chloroacetophenone (23.0), 3′,4′-dimethoxyacetophenone (25.2), 3′-bromo-4′-methoxyacetophenone (25.1), and the highly substituted 3′-chloro-5′-methoxy-2′,4′-dimethylacetophenone (24.3). These few examples show the power of our approach in allowing pK_a data to be obtained rapidly and easily.

A limiting factor when using the in situ Raman monitoring methodology is that the reaction mixture must remain homogeneous throughout the course of the reaction as well as at all temperatures investigated. If a precipitate begins to form, the path length of the laser is no longer a constant and converting units of Raman intensity to concentration will no longer be reliable. The reaction between 3′-chloroacetophenone and benzaldehyde was investigated. Figure 4 shows an overlay of the first 5 scans of the reaction and the inset depicts the first 15 scans in the region of 1500−1700 cm^{-1}. Two aspects are immediately apparent. First, the large negative peaks at 882, 1001, 1049, 1094, and 1453 cm^{-1} are due to loss of the signal of the solvent, ethanol. In none of the other reported chalcone syntheses did we observe this phenomenon. Second, the Raman signal growing in at 1602 cm^{-1} is much less intense than had been observed for other chalcones (Figure 4, inset). We believe that the rapid drop in intensity of the solvent signal as well as the low Raman signal intensity for the α,β-unsaturated ketone upon catalyst injection arises from the slight insolubility of an intermediate

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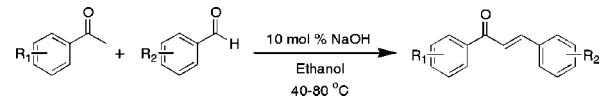
Table 1. Observed Activation Enthalpies ($\Delta H^{\ddagger}$) for the Formaton of Substituted Chalcones



entry	R_1	R_2	$\Delta H^{\ddagger}$ (kJ/mol)
1	−H	−H	49.0
2	4-Cl	−H	39.8
3	2-Cl	−H	33.6
4	−H	4-Cl	48.3
5	−H	2-Cl	61.2
6	4-Ph	−H	46.6
7	4-OCH_3	−H	59.6
8	4-OCH_3	4-OCH_3	59.2
9	4-F	−H	49.9
10	4-CH_3	−H	51.5
11	3,4-$(OCH_3)_2$	−H	54.5
12	3-Br-4-OCH_3	−H	54.2
13	3-Cl-5-OCH_3-2,4-$(CH_3)_2$	−H	46.2
14	2-acetylpyridine	−H	40.2

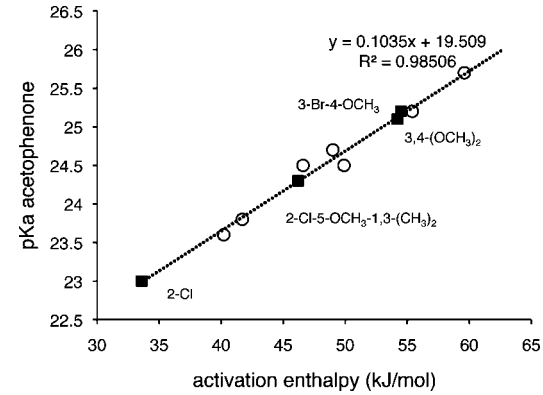


Figure 3. Plot of known pK_a values of acetophenones (○) versus calculated activation enthalpies for the aldol condensation with benzaldehde. Extrapolated pK_a values (■) for 2′-chloroacetophenone (23.0), 3′,4′-dimethoxyacetophenone (25.2), 3′-bromo-4′-methoxyacetophenone (26.0), and 3′-chloro-5′-methoxy-2′,4′-dimethylacetophenone (25.1) based upon the best-fit line, $y = mx + b$; $m = 0.104$, $b = 19.51$; $R^2 = 0.985$.

along the reaction pathway. The resultant cloudy solution shortens the path length of the laser, and results in inprecise intensity data being recorded. Furthermore, as solubility is dependent upon temperature, the intermediate is most likely more soluble at high temperatures than at lower ones, leading to a longer effective path length at elevated temperatures and thus limiting our ability to extract quantitative kinetic data.

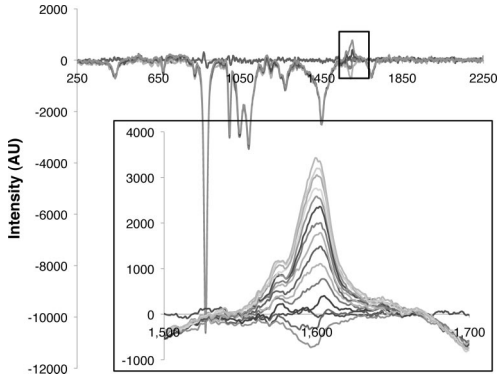


Figure 4. Overlay of the first five Raman spectra generated while monitoring the condensation between 3′-chloroacetophenone and benzaldehyde. The large negative peaks are due to signal loss of the ethanol solvent and indicate loss of effective path length. Inset: The first 15 scans of the reaction in the region of 1500−1700 cm^{-1}. The low signal strength due to the formation of the chalcone also indicates a shortened path length.

Despite these problems, since the pK_a data are known for 3′-acetophenone, we continued to probe the reaction using this substrate to test our reasoning that insolubility would be a larger factor at low temperatures, hence leading to a larger negative slope in the derived Eyring plot. As predicted, the plot of ln(*k*/*T*) vs 1/*T* (Figure 5) leads to a calculated activation enthalpy of 46.8 kJ/mol, significantly higher than the expected value of 34.8 kJ/mol determined from Figure 3 by using the known pK_a value of 23.2 for 3′-chloroacetophenone.

In summary, this work shows the scope and limitations when using Raman spectroscopy as a method to determine

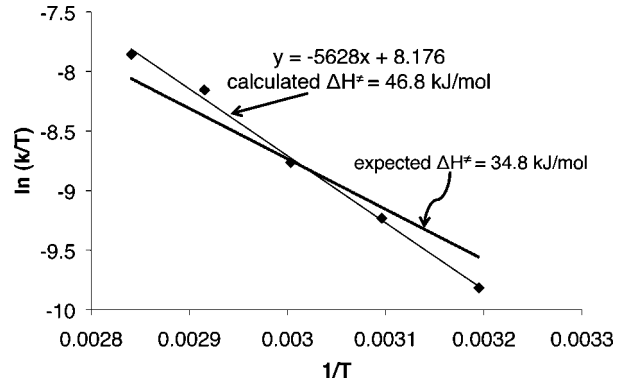


Figure 5. Erying plot for the formation of 3′-chlorochalcone. Calculated activation enthalpy (46.8 kJ/mol) deviates from the expected value (34.8 kJ/mol) due to the heterogeneous reaction conditions upon addition of the catalyst.

kinetic data for organic reactions. We were able to determine the activation enthalpies for the formation of a number of substituted chalcones and were able to show that our results correlate well with known pK_a data. This shows the vailidity of our methods. A limiting factor, however, is that the reaction mixture must remain homogeneous throughout the course of the reaction to be able to obtain accurate data. Current work is underway to exploit this technique further and to examine other, less well-characterized, organic reactions.

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Supporting Information Available: Apparatus overview, detailed experimental procedures, and copies of ^1H and ^{13}C NMR of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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