Organic Process Research & Development

ARTICLE

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Kinetic Understanding Using NMR Reaction Profiling

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ABSTRACT: The combination of kinetic understanding and reaction modeling has been successfully applied to the development of processes from laboratory to manufacturing plant. Although extensively used in bulk chemistry, polymers, and the oil industry [Bayer Technology Services, http://www.bayertechnology.cn/uploads/media/0707_e_300dpi.pdf, July 2011; Lawrence Livermore National Laboratory, http://www1.eere.energy.gov/vehiclesandfuels/pdfs/merit_review_2011/fuel_technologies/ft010_pitz_2 011_o.pdf, July 2011; Shin, S. B.; Han, S. P.; Lee, W. J.; Chae, J. H.; Lee, D. I.; Lee, W. H.; Urban, Z. *Hydrocarbon Process.* **2007**, April, 83; Baumer, C.; Urban, Z. *Hydrocarbon Process.* **2007**, June, 71], it has not been exploited to its full potential in the pharmaceutical industry. We present a fast and efficient methodology for kinetic modeling of chemical reactions using ^{1}H NMR reaction monitoring that can be used for the process understanding and development of active pharmaceutical ingredients. The parameters that are important for the development of a good, reliable model for the prediction and optimization of reaction conditions are discussed. The hydrolysis of acetic anhydride was chosen to illustrate the methodology because it is mechanistically and kinetically well established.

INTRODUCTION

Reaction modeling using NMR data has been the subject of multiple research papers.[5−7] NMR together with *in silico* methods is a powerful tool for the study of reaction kinetics. NMR spectroscopy provides structurally rich data, from which it is possible to confirm or elucidate the structure of starting materials, intermediates, and products.[8] It is intrinsically quantitative, overcoming the need to determine response factors required by other techniques such as HPLC. It is not intrusive, and it is potentially able to detect every compound involved in the reaction provided NMR active nuclei are present and there is sufficient signal dispersion. Despite its power, NMR is not the technique of choice in pharmaceutical process development.[9] Even in the early stages of development, reaction monitoring by NMR tends to be only sporadically used by NMR and/or chemical engineering specialists. Nevertheless, the pharmaceutical industry is giving increased levels of attention to reaction understanding as a way to ensure the quality of the active pharmaceutical ingredient (API) and manufacturing process robustness throughout its entire lifecycle.

The mechanism of the hydrolysis of acetic anhydride has been extensively studied during the last century.[10] The intermediate scheme proceeds *via* three irreversible steps: addition of water, elimination, and proton transfer (Scheme 1), the addition being the rate-limiting step.[11]

$$Ac_2O + H_2O \rightarrow 2AcOH \quad \text{(I)}$$

$$-d[Ac_2O]/dt = k[Ac_2O]\cdot[H_2O] = A\cdot e^{-E_a/RT}\cdot[Ac_2O]\cdot[H_2O] \quad \text{(II)}$$

$$k = A\cdot e^{-E_a/RT} \quad \text{(III)}$$

The overall reaction can be represented in a simplified eq I. The rate of hydrolysis, $-d[Ac_2O]/dt$, can be expressed as a function of the concentration of both starting material ($[Ac_2O]$) and reagent ($[H_2O]$), eq II. The Arrhenius eq III gives the dependence of the rate constant (k) of hydrolysis on the temperature (in Kelvin) and activation energy (E_a), A being the pre-exponential Arrhenius factor and R the gas constant.

In the conditions of a high excess of water, the hydrolysis of acetic anhydride can be considered to be pseudo-first-order, simplifying the kinetic parameters calculation. The integrated rate law can be rearranged such as the eq IV where $[Ac_2O]_0$ is the initial concentration of acetic anhydride. Plotting $\ln[Ac_2O]/[Ac_2O]_0$ against time creates a straight line with slope $-k$. This can be repeated for different temperatures. From the Arrhenius eq V, a plot $\ln k$ versus $1/T$ produces a straight line where E_a and $\ln A$ can be determined from the slope and the intercept.

$$\ln[Ac_2O]/[Ac_2O]_0 = -kt \quad \text{(IV)}$$

$$\ln k = -E_a/RT + \ln A \quad \text{(V)}$$

First-order reactions are rare in the pharmaceutical industry. Therefore, in this study we treated the hydrolysis of acetic anhydride as a second-order type of reaction to demonstrate our methodology for more general application.

In this contribution, the kinetic parameters A and E_a were calculated using Dynochem[12] from a series of experiments including variation of (1) initial concentrations of reagents and (2) the reaction temperatures. ^{1}H NMR was used to monitor the evolution of starting material and product concentration as a function of time.

Received: August 1, 2011
Published: October 26, 2011

dx.doi.org/10.1021/op200202k | *Org. Process Res. Dev.* 2012, 16, 61–64

Scheme 1. Mechanism of acetic anhydride hydrolysis by water

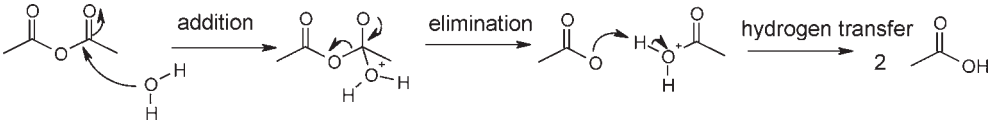

Table 1. Summary of experimental reaction conditions and NMR acquisition parameters[a]

		temperature (°C)		D_2O	acetic anhydride		acquisition	
N	t_0	bath	spectrometer	V (μL)	mass (mg)	[ ] (M)	pad (min)	total (h)
1	~5′	24.8	25	750	78.0	0.91	1	1
2	~5′	14.8	15	750	77.9	0.91	2	3
3	5′ 5″	5.0	5	750	77.7	0.91	10	10
4	4′15″	24.5	25	750	38.4	0.47	1	2
5	4′19″	24.9	25	750	19.2	0.24	2	4

[a] N = experiment number, t_0 = time between initiation of the reaction and starting the acquisition, V = volume, [ ] = concentration, pad = pre-acquisition delay.

EXPERIMENTAL SECTION

The reaction was performed at different concentrations and temperatures (Table 1). Each reaction was prepared by the addition of an appropriate amount of acetic anhydride and 750 μL of deuterium oxide (D_2O) into a test tube placed in an oil bath set at the required temperature. They were then mixed in the test tube, transferred to a 5 mm NMR tube, also at the same temperature, and immediately placed in the NMR spectrometer (Varian Inova 500 MHz equipped with a 5 mm triple-resonance ($^1H/^{15}N/^{13}C$) probe), set at the same temperature as that of the bath. Once in the NMR spectrometer, the homogeneity of the magnetic field was adjusted by gradient shimming on the z-axis, and an array of ^1H experiments was acquired. The probe had previously been tuned and matched with a sample of similar composition. The delay between initiation of the reaction and starting acquisition was accurately measured for most of the reaction conditions (Table 1). The duration of the pulse program was also taken into account to obtain an accurate time value. The course of the reaction was followed by ^1H NMR. Key parameters are contained in Table 1.

Data were processed and analyzed using MestReNova, 6.1.1, build 6384 (MestreLab Research). The regions of interest were integrated, and the values obtained were transferred to Dynochem (3.2.1.0) in order to build a kinetic model.

RESULTS AND DISCUSSION

NMR experiments were acquired as described in the Experimental Section. The experiments were designed to cover a wide range of concentration of substrate and of temperature to enable a good understanding across a large design space. Two peaks were observed in the spectra (Figure 1): one depleting and the other increasing with time. They correspond to the methyl protons of the acetic anhydride (2.19−2.03 ppm) and acetic acid (2.01−1.86 ppm), respectively. These two regions were integrated, and the values of the integrals were converted to moles.

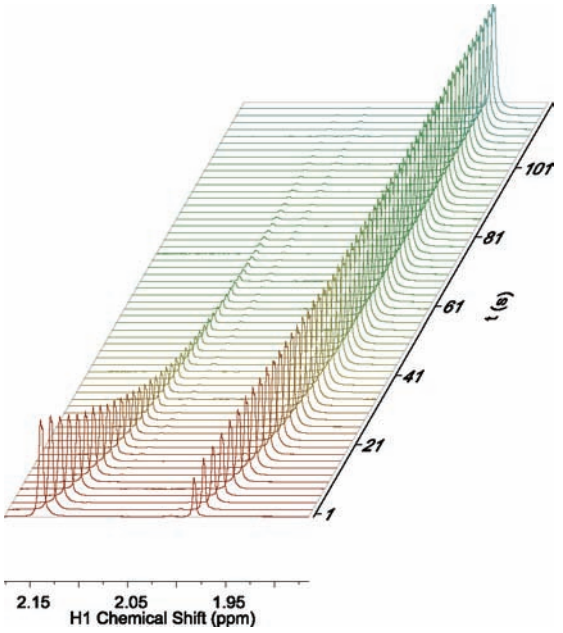

Figure 1. ^1H NMR spectra (aliphatic region expansion) of the acetic anhydride (0.47 M, 25 °C) hydrolysis vs number of scan (s). The peaks correspond to the methyl protons of the acetic anhydride (left) and the acetic acid (right).

Dynochem was chosen to build a kinetic model based on the rate eq II, which describes the hydrolysis of the acetic anhydride assuming first-order kinetics for both acetic acid and water concentration. E_a and A are adjustable kinetic parameters.

The time-resolved experiments (time vs concentration) for different conditions were imported into the program and were used to solve the rate equation and calculate the optimum value for E_a and A. The Levenberg−Marquardt fitting algorithm was used, which calculates different theoretical reaction profiles by iterating E_a and A, and looks for the minimal deviation between calculated and experimental data. This is expressed as the sum of the squares deviation (SSQ) in eq VI where j is the experiment number, M the number of experiments, i the point number and N the number of points, $(y_{ij} - y_{jmod})$ is the difference between experimental and calculated values and w_j a weighing factor for each of the different experiments.

$$\mathrm{SSQ} = \sum_{j=1}^{M} w_j \sum_{i=1}^{N} (y_{ij} - y_{ijmod})^2 \qquad \text{(VI)}$$

The program reports the best values for E_a and A after convergence or after a predefined maximum number of iterations. E_a and A are reported with an associated confidence interval, expressed as a percentage of the parameter value.

In the case of the acetic anhydride hydrolysis, values of ln $A = 8.05 \pm 1.02\ s^{-1}$ and $E_a = 11.4 \pm 0.4$ kcal/mol were obtained

dx.doi.org/10.1021/op200202k |Org. Process Res. Dev. 2012, 16, 61–64

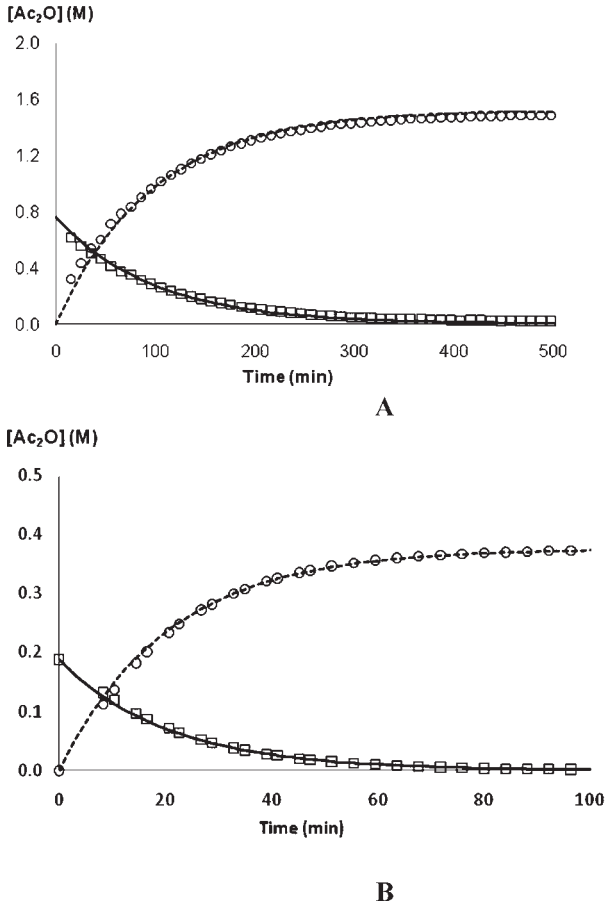

Figure 2. Reaction profile for experiments 3 and 5 conducted respectively with 0.91 M acetic anhydride at 5 °C (A) and 0.24 M at 25 °C (B). The depletion of acetic anhydride is represented with squares, and the formation of acetic acid, with circles. The solid and dotted lines represent the prediction calculated by Dynochem.

Table 2. Experimental activation energies and ln *A* values for the acetic anhydride hydrolysis

	activation energy (kcal/g mol)	ln *A* (L/(g·mol·s))
this work	11.4	8.05
Asprey et al.[11]	10.9	7.66
Glasser and Williams (1971)[13]	10.8	7.95
Cleland and Wilhelms (1956)[14]	10.6	7.80
Eldridge and Piret (1950)[15]	10.3	7.53

after 400 iterations. The confidence interval for both was <10%, which is considered to be very good. The quality of the fit is illustrated in Figure 2, which show a high degree of overlap between calculated and experimental reaction profiles for the reaction at 25 °C and acetic anhydride initial concentrations of 0.91 and 0.24 M.

The value of the kinetic parameters E_a and ln *A* obtained for the acetic anhydride hydrolysis using the methodology reported in this contribution are also in good agreement with the values reported in the literature[16,17] for the same reaction, but using different techniques (Table 2).

Kinetic studies require accurate measurement and control of reaction conditions. Factors that could contribute to the experimental error within this study are the failure to accurately control the temperature throughout the reaction, which is especially important in nonadiabatic reactions, and the failure to accurately measure the total reaction volume, which is not necessarily the sum of reagent volumes. The accurate measurement of the mass of reagents is also important. This is especially difficult when working on a small scale.

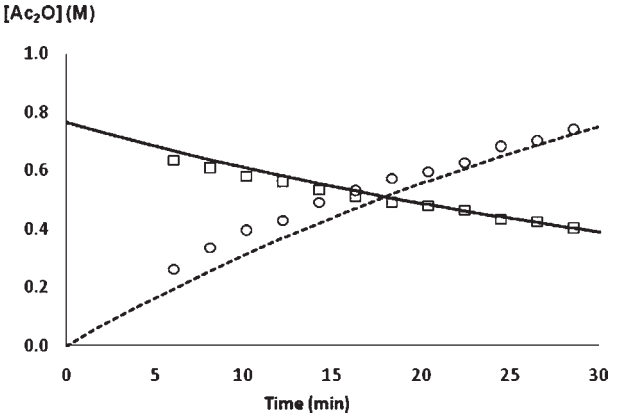

Figure 3. Reaction profile for experiment 2 conducted with 0.91 M acetic anhydride at 15 °C. The depletion of acetic anhydride is represented with squares, and the formation of acetic acid, with circles. The solid and dotted lines represent the prediction calculated by Dynochem.

Figure 2 shows the reaction profiles for experiments 3 and 5 with good agreement between experimental and calculated values. The agreement is not as good in experiment 2 (Figure 3). In this last case the delay between initiation of the reaction and starting the NMR acquisition was not as accurately measured as in the experiments 3, 4, and 5, and this is the root cause of the poorer fit of the experimental and calculated data.

The methodology described in this contribution has some limitations and would not be the method of choice for the direct study of biphasic systems or of very fast or exothermic reactions because of issues of nonhomogeneity of the sample, the need to mix all reagents and solvents outside of the NMR magnet, and the lack of good temperature control throughout the whole duration of the experiments, respectively. However, it has the potential to be widely applied to pharmaceutical process chemistry projects because it is inherently quantitative, simple, fast, and easy to use. It also provides structural information which can assist the identification of intermediates. The authors believe that a model does not necessarily have to be built with experimental data derived from large-scale reaction conditions or from mimicking large-scale conditions (e.g., kilo lab and pilot plant). It can be built during the small-scale experimental design stage for use in reaction understanding and optimization. The chemical model so developed will then be in place and ready to combine with the reactor modelling data for use in supporting process scale-up.

■ CONCLUSIONS

A kinetic model was derived from NMR experiments for the hydrolysis of acetic anhydride with water. The results demonstrate that ^{1}H NMR data obtained by monitoring reactions in an NMR tube can be sufficient to build a good, reliable kinetic model, provided the experiments are conducted in a controlled

dx.doi.org/10.1021/op200202k |*Org. Process Res. Dev.* 2012, 16, 61–64

manner with high attention to detail. It is important to accurately measure the mass of the starting materials and solvents together with the time delay between the initiation of the reaction and the start of the NMR acquisition. It is also critical to control the temperature during the preparation of the sample and throughout the reaction in order to minimize experimental errors.

Despite NMR being a very powerful and widely available technique, we believe that it is underutilized in the chemical process development arena. It has great potential value for kinetic modelling in combination with orthogonal data from other techniques (such as LC, GC, or IR).

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ACKNOWLEDGMENT

We thank Santiago Dominguez and Carlos Cobas (Mestrelab Research) for software support and development and Joe Hannon (Dynochem), Christopher Pilkington and Pfizer colleagues (Wilfried Hoffmann, Julian Smith, Don Richards) for useful discussions.

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