

Learning Chemistry from Good and (Why Not?) Problematic Results: Kinetics of the pH-Independent Hydrolysis of 4-Nitrophenyl Chloroformate

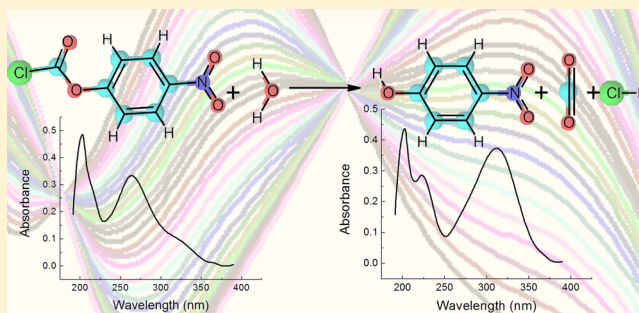
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S Supporting Information

ABSTRACT: The determination of kinetic data is central to reaction mechanism; science courses usually include experiments on chemical kinetics. Thanks to PC-controlled data acquisition and availability of software, the students calculate rate constants, whether the experiment has been done properly or not. This contrasts with their experience in, e.g., organic synthesis, where a broad melting point indicates an impure product. In order to teach quality kinetics and link theory to experiment, we used a multistep project, based on the (convenient) pH-independent hydrolysis of 4-nitrophenyl chloroformate in aqueous organic solvents. The steps of the project included statement of the experiment's objective; a quiz on reaction mechanism and experimental techniques in chemical kinetics; students' decision on the organic solvent to be employed; extraclass activity to assess their choice of the solvent; carrying out the experiment; and discussion of the results obtained. We have applied the constructivist approach to illustrate that controlling the experimental conditions (solution temperature and homogeneity) is a prerequisite for obtaining quality kinetic data. The students' evaluation was highly positive because they participated in the different steps of the project.

KEYWORDS: Upper-Division Undergraduate, Organic Chemistry, Physical Chemistry, Hands-On Learning/Manipulatives, Esters, Kinetics, Reactions, UV–Vis Spectroscopy



INTRODUCTION

Most of our knowledge about reaction mechanism came from, and still comes from, kinetic data. Therefore, chemistry courses for science students include experiments on chemical kinetics, e.g., catalyzed acyl transfers^{1–3} and sugar reactions.⁴ In addition to acquiring practical skills, the students attach much importance to linking theory to experiment.⁵ Representative examples of this approach include the introduction of thermodynamic versus kinetic control of reactions⁶ and the interplay between chemistry and visual art.⁷

Chemical kinetics experiments can be deceptively simple, especially because data acquisition is mostly done by PCs and software is available to calculate rate constants. This convenience may tempt a few students to use a “black-box” approach: mix the reagents, acquire experimental data, and then calculate the results. Therefore, they are usually able to calculate rate constants, independent of their quality. Some may not give proper attention to eventual problems with data fit, e.g., the agreement between the calculated “infinity” reading and the experimentally determined one; the magnitude and variation of the residuals (differences between experimentally and theoretically calculated data points, e.g., by iteration) with time (t). Ideally, the residuals should be small and vary randomly with t .

To illustrate this situation, compare two aspects of acetyl-salicylic acid (aspirin), namely, its synthesis (organic chemistry laboratory) and hydrolysis (physical chemistry laboratory). In synthesis, the student assesses the outcome of his or her work by comparing *any* of the following product properties with literature data: mp 135 °C; IR spectroscopy ($\nu_{\text{C=O}}$ peak of the acetyl group at ca. 1754 cm^{-1}); ^1H NMR spectroscopy ($\text{CH}_3\text{CO}-$ peak, at 2.352 ppm).⁸ Hydrolysis of aspirin requires attention because it is subject to general acid–base catalysis; its rate constant depends on the temperature (T); solution pH; and the nature and concentration of the buffer.^{9–13} If the student does not control the first two experimental variables properly, the calculated rate constants may appear in order if examined for a single run. The problem appears, however, when the data from different students are employed jointly, e.g., in plots of observed rate constant, k_{obs} , versus catalyst concentration, or $\log k_2$ (second-order rate constant) versus $1/T$ (Arrhenius plot).

When this problem occurs, the student may feel frustrated, justifiably so especially because repeating the experiment may not be feasible. Obtaining *quality* kinetic data, therefore, requires attention because the effect of problems, if they do

Table 1. Summary of the Project Steps

Step	Class Time/h	Exercise
1	None	Two weeks before the experiment, the instructor explained the objective of the project: As an example of acyl-transfer reactions, the class will study the kinetics of ester hydrolysis in m-solvent, using UV-vis spectroscopy. The students were asked to read about mechanism of acyl transfer reactions and chemical kinetics.
2	2	One week before the experiment, the students answered a quiz, and decided on the organic component of the m-solvent.
3	None; off-class activity	Two groups of students used the laboratory in off-class hours to record absorbance versus wavelength as a function of time for the hydrolysis of NPCF in m-solvents.
4	4	Four groups of students studied the effect on k_{obs} of temperature (15, 25, 31, and 45 °C, aqueous MeCN; $[\text{H}_2\text{O}] = 11.08 \text{ mol L}^{-1}$); four groups determined the kinetic order with respect to water (10.1, 11.6; 12.9, 16.0, and 20.0 mol L^{-1} , in MeCN, at 25 °C).
5	None	The students exchanged their data and calculated the rate constants and activation parameters.
6	2	The students presented the effects of the following variables on k_{obs} : $[\text{H}_2\text{O}]$; T ; organic component of the m-solvent. The results obtained were discussed in class.

occur, is not perceptible while the experiment is being done. It is worthwhile to remember Bunnett's warning "good chemists have gotten into trouble in kinetics work, and you can too if you aren't careful".¹⁴

With this background in mind, we have introduced an interdisciplinary project on the pH-independent hydrolysis of 4-nitrophenyl chloroformate (NPCF) in binary mixtures of water and acetonitrile, MeCN, or dimethoxyethane, DME. The project integrates physical and organic chemistry and is used to teach both theory (acyl-transfer reactions, solvent effects, activation parameters) and practical kinetics (obtaining quality rate data). The students appreciated our use of the constructivist approach, as well as their participation in decision making regarding the experimental variables.

EXPERIMENTAL SECTION

We purchased the chemicals from Alfa-Aesar. The staff purified MeCN and DME by distillation from CaH_2 ; NPCF by sublimation under reduced pressure, and prepared the ester stock solutions in dry MeCN or DME ($(1-3) \times 10^{-4} \text{ mol L}^{-1}$). The students prepared all aqueous mixed solvents (hereafter designated as "m-solvents") by volume by using precision buret; the m-solvents contained 0.001 mol L^{-1} HCl (see note SI-1 in the Supporting Information).

Kinetic runs were performed with Zeiss PM6KS and Hewlett-Packard HP-8453 UV-vis spectrophotometers (note SI-2 in the Supporting Information), provided with cell holders whose temperature was controlled by water circulation from thermostats. The runs were initiated by injecting 10 μL of the ester stock solution into 1 mL of the m-solvent, and the solution was homogenized for a few seconds with a hand-held, battery-operated microstirrer (model 338.004, Hellma); the cuvette was stoppered, and the increase in absorbance (A_t) as a function of time (t) at wavelength $\lambda = 320 \text{ nm}$ (due to liberation of 4-nitrophenol) was monitored until the absorbance was practically constant ("infinity" reading, A_∞).

From the absorbance (A_t) and the corresponding time (t) the students first calculated A_∞ with a nonlinear regression analysis program;¹⁵ theoretically calculated and experimental A_∞ agreed within 2%. Next they calculated the value of k_{obs} , in s^{-1} , from the slope of the $\ln(A_\infty - A_t)$ versus t plot, and k_2 , in $\text{L mol}^{-1} \text{ s}^{-1}$, by dividing k_{obs} by $[\text{H}_2\text{O}]$.

In an off-class activity, the reaction progress was monitored in the 220–400 nm range as a function of (t) with a Shimadzu UV-2500 spectrophotometer.

HAZARDS

MeCN and DME are flammable and are slightly toxic; NPCF may cause eye and respiratory irritation and skin burning.

The students manipulated all chemicals and prepared the m-solvents in a fume-hood.

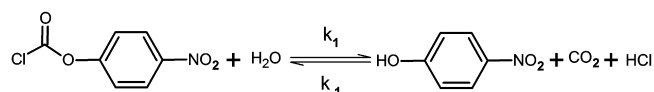
RESULTS AND DISCUSSION

Steps of the Project

This project was part of a spectroscopy course (Chem-2144), given to chemistry-major students in their 5th semester. The class (66 students) was divided into 8 groups. Table 1 summarizes the steps of this project.

Step 1 of the activities was merely informative. In the quiz given (step 2; SI-3 in the Supporting Information), we showed the reaction scheme, Scheme 1, and asked the students to

Scheme 1. Hydrolysis of Nitrophenyl Chloroformate (NPCF)



(i) write down its mechanism; (ii) discuss a technique (other than UV-vis) that can be employed to follow reaction progress; (iii) choose a solvent from a list of *water-miscible* liquids; and (iv) discuss an acyl-transfer reaction relevant to an everyday situation.

The students rejected alcohols because their use leads to two parallel reactions (with water and ROH); they chose two solvents MeCN and DME; 67% suggested the use of conductivity in order to follow the hydrolysis of NPCF (increase in conductivity due to liberation of HCl). All students selected trans-esterification for making biodiesel as an important example of acyl-transfer reactions. The reason for this unanimity is that in Brazil the use of bioethanol as fuel additive for gasoline dates back to 1931; biodiesel is, by law, a component of petroleum-based diesel oil.

We agreed with the students' decision to use two m-solvents, provided that the reaction in both media is complete within one 4 h laboratory period. To assess reaction time, two groups of students used the laboratory in off-class hours to register absorbance versus λ as a function of time (4 mol L^{-1} water–MeCN or water–DME). Based on Figure 1, the students concluded that both m-solvents can be used; $\lambda_{\text{max}} = 320 \text{ nm}$ is appropriate for monitoring reaction progress (step 3).

In step 4, four groups studied the effect of temperature (15, 25, 31, and 45 °C; aqueous MeCN; $[\text{H}_2\text{O}] = 11.08 \text{ mol L}^{-1}$); four groups determined the kinetic order with respect to water (10.1, 11.6; 12.9, 16.0, and 20.0 mol L^{-1} , in MeCN, 25 °C). For each group, the instructor carried out the first kinetic run,

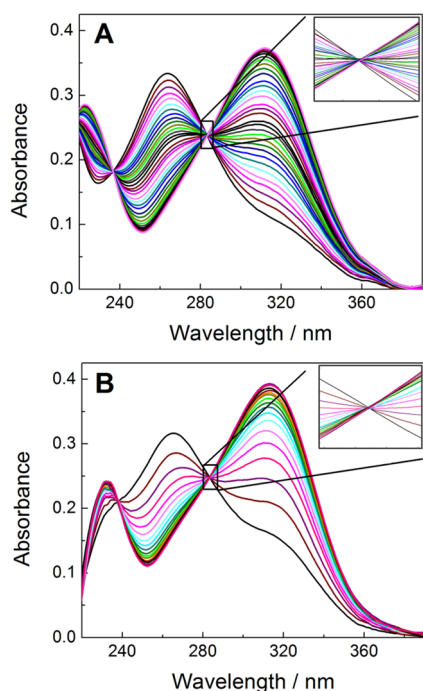


Figure 1. Absorbance versus wavelength, λ , as a function of time (t) for the hydrolysis of NPCF, at 25 °C, in the presence of 4 mol L⁻¹ water in MeCN (part A) or DME (part B). The time intervals between pairs of successive scans are ca. 1 and 2 min, respectively. The insets show the isosbestic points of the reactions in the corresponding solvents.

where the experiment was done by using, *deliberately*, a faulty procedure (no thermostating), but without telling them. This was done as follows: The instructor explained how the spectrophotometer works, what the program commands required for data acquisition are, and how the experiment will be carried out. During this explanation time, the instructor *deliberately* kept the cuvette out of the thermostated cell holder. Consequently, this demonstration experiment was started at room temperature, and not at 40 °C. During the explanation time, however, the two cuvettes that would be used by the students were kept in the cell holder, i.e., the students ran their experiments properly (T control). After finishing their experiments and calculating the values of k_{obs} , the students exchanged their data and calculated further results (second order rate constants; kinetic order with respect to water, and activation parameters; step 5; note SI-4 in the Supporting Information). Step 6 included a discussion of the data obtained.

Figure 2 shows the rate constants calculated by the students, as compared with published data;¹⁶ the agreement is satisfactory.

Learning from “Problematic” Data: Different Reaction Conditions Give Different Results

Importance of Temperature Control. The students’ data shown in Figure 2 are average values. As given in the Experimental Section, the instructor did the first experiment; the students ran a duplicate afterward. In order to stress the importance of T control, the instructor ran the demonstration experiment by using cuvettes that were not thermostated. For *each temperature*, therefore, they calculated three k_{obs} ; the value of k_{obs} for the first (demonstration) was always smaller than the other two (done by the students); see Table 2.

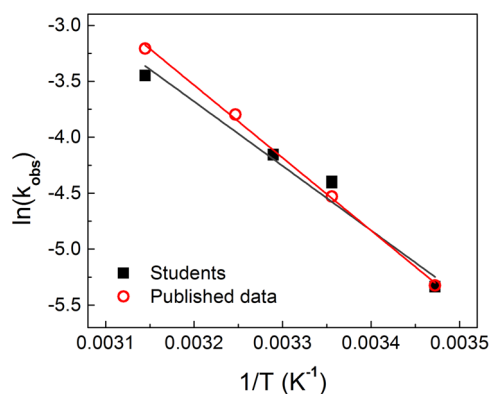


Figure 2. Arrhenius plots for hydrolyses of NPCF in MeCN, [H₂O] = 11.08 mol L⁻¹. Students’ results are listed in Table SI-1 in the Supporting Information.

Table 2. Hydrolysis of NPCF in 5.10 mol L⁻¹ H₂O in MeCN, at 40 °C^{a,b}

No Temperature Control			Proper Temperature Control, $T = 40$ °C		
Run	$k_{\text{obs}} \times 10^3, \text{s}^{-1}$	$t_{1/2} \text{ (s)}$	Run	$k_{\text{obs}} \times 10^3, \text{s}^{-1}$	$t_{1/2} \text{ (s)}$
NT1	3.49	198.6	T1	3.84	180.5
NT2	3.42	202.6	T2	3.86	179.5
NT3	3.47	199.7	T3	3.85	180.0

^aNT, T, and $t_{1/2}$ stand for no and proper T control and the reaction half-life, respectively. ^bThe dependence of k_{obs} on T is listed in Table SI-1 in the Supporting Information.

They considered their duplicate because both values of k_{obs} agreed, i.e., discarded the demonstration result. We probed the origin of this difference. After some inconclusive discussion, we explained how we did the experiment, i.e., the origin of the smaller (k_{obs}) is that the starting conditions were different; this underlined the importance of controlling T .

Importance of Solution Homogeneity. During step 6, we asked the students to comment on Figure 3, where the effect of solution homogeneity on the quality of fit to the kinetic data is shown. The staff carried out these experiments in an off-laboratory period, as follows: in experiment A the cuvette remained in the cell holder; its stopper was removed; the ester was injected; the mixture was not agitated. In run B the cuvette remained in the cell holder; its stopper was removed; the ester was injected; the solution was stirred for few seconds with a hand-held microstirrer. In run C the cuvette was removed from the cell holder; its stopper was removed; the ester was injected; the cuvette was shaken by hand for few seconds, and then put back into the cell holder. The students appreciated the importance of solution homogeneity to obtain good results. Lack of mixing resulted in bad fit to the data and relatively large residuals (part A). Part C shows that stirring by hand is good enough; the advantage of using the microstirrer (run B) is that the cuvette is not removed from the cell holder, i.e., solution temperature is maintained constant.

Learning Theory from Experiment. Based on linear $\ln(A_{\infty} - A_t)$ versus t plots for all [H₂O] and Figure 4, the students concluded that the reaction is second order overall, first order in ester and water (this simple conclusion does not hold, however, over a larger water concentration range).¹⁶

From the isosbestic points shown in Figure 1, 238 and 282 nm for both m-solvents, they concluded that the

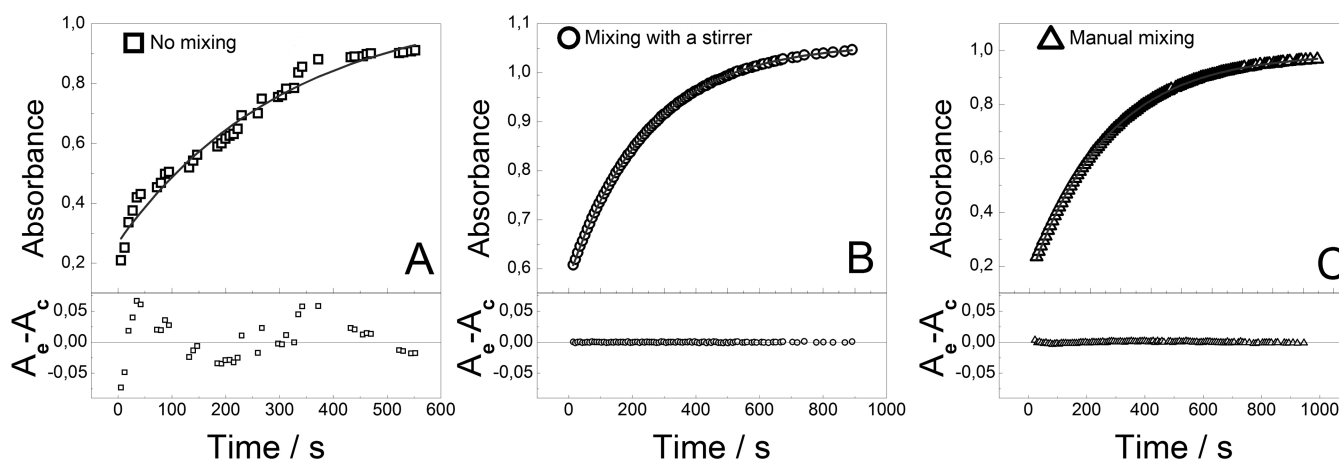


Figure 3. Effect of reactant mixing. In run A the ester was injected; the mixture was not agitated. In runs B and C the ester was agitated by a microstirrer or by hand, respectively; A_e and A_c are experimental and calculated absorbance, respectively. The solid curve shown in A is theoretical.

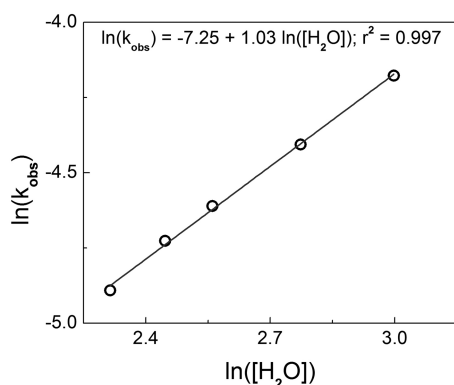


Figure 4. Effect of $[H_2O]$, 10–20 mol L⁻¹, on k_{obs} for the hydrolysis of NPCF in MeCN, at 25 °C. The slope (1.03) is the kinetic order with respect to H_2O .

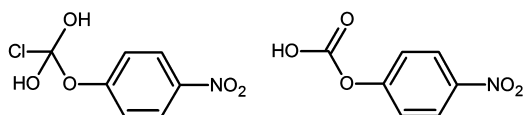


Figure 5. Reactive intermediates of the hydrolysis of NPCF.

Table 3. Activation Parameters Calculated at 25 °C for the Hydrolysis of NPCF in 2.47 mol L⁻¹ Water in MeCN^{a,b} or in DME^b

Solvent	$\Delta E^\ddagger$ / kcal mol ⁻¹	$\Delta H^\ddagger$ / kcal mol ⁻¹	$-T\Delta S^\ddagger$ / kcal mol ⁻¹	$\Delta G^\ddagger$ / kcal mol ⁻¹
Water–MeCN	9.2 ± 0.1	8.6 ± 0.1	14.6 ± 0.1	23.2 ± 0.1
Water–DME	7.5 ± 0.1	6.9 ± 0.1	14.1 ± 0.1	21.0 ± 0.2

^aThese values were obtained by interpolation from the data published elsewhere.¹⁶ ^bThe dependence of k_{obs} on T is listed in Table SI-2 in the Supporting Information. The activation parameters are based on $k_2 = k_{obs}/[H_2O]$.

intermediates formed, Figure 5, do not accumulate (otherwise no isosbestic point should have been observed).¹⁶

To explain the faster reaction in aqueous DME, relative to that in aqueous MeCN, the students compared the activation parameters at the same $[H_2O]$, see Table 3.

The reaction in aqueous DME is faster due to favorable enthalpy and entropy of activation. A suggestion is given in

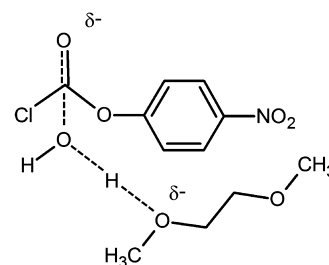


Figure 6. Suggested transition state structure for the hydrolysis in aqueous DME. The latter is acting as a “general base” for the attacking water molecule, leading to faster reaction.

Figure 6, where the ether oxygen of DME is acting as a general base for water attack on the acyl group.¹⁶ We then handed out an evaluation sheet, which students returned a week later (note SI-5 in the Supporting Information).

CONCLUSIONS

We have employed a project to teach theory (reaction mechanism; solvent effects on reactivity; activation parameters) and demonstrate important practical aspects of chemical kinetics. Examination of the residuals is an essential tool to ensure quality kinetic data. The experiment's versatility stems from the fact that the value of k_{obs} can be controlled by adjusting $[H_2O]$ and T . It is simple because it required little preparation; no buffers. No dangerous chemicals are employed; a very small volume of aqueous liquids needs to be discarded (safety). As shown in note SI-5 in the Supporting Information, the students' evaluation sheets indicated that they have enjoyed the constructivist approach, even if it means working “overtime”.

ASSOCIATED CONTENT

Supporting Information

Notes explaining how the experiment was carried out (SI-1), the equipment employed (SI-2), the questions given in the quiz (SI-3), calculation of the kinetic data (SI-4), and the student's evaluation of the experiment (SI-5). Two tables listing the values of k_{obs} for hydrolyses of NPCF in aqueous MeCN (Table SI-1) and the dependence of k_{obs} on the temperature for ester hydrolysis in MeCN and DME (Table SI-2). Notes for the instructor. This material is available via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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