Class Projects in Physical Organic Chemistry: The Hydrolysis of Aspirin

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The hydrolysis of aspirin is studied in a third-year organic chemistry course (Chemistry 337, Bioorganic Chemistry) at the University of Victoria. The topic is studied in the lecture and laboratory as a means of understanding catalysis and how a change in pH can affect reaction rates and the mechanism of hydrolysis. The exercise presented provides a hands-on demonstration of the hydrolysis of aspirin. The students are able to see the correlation between their results obtained in the laboratory and the mechanisms discussed in the lecture. This correlation leads to a greater understanding of the mechanisms of catalysis and the utility of the pH–rate profile for determining these mechanisms.

The hydrolysis of aspirin was studied in detail by L. J. Edwards in 1950 *(1).* Others have studied the hydrolysis of salicylates and similar compounds *(2);* however, this experiment is based on Edwards' work. Several experiments have been described in this *Journal* on catalysis and hydrolysis *(3),* but only two *(4)* have considered pH–rate profiles and both of these experiments involved enzymatic hydrolysis. This experiment examines the catalysis of hydrolysis in a purely chemical system over a wide pH range and can be used in courses on bioorganic chemistry, physical organic chemistry, and chemical kinetics.

The experiment is presented as a class project. A student's data points (pH and corresponding rate constant) are collected by the course coordinator who provides the complete data set to the entire class. Access to the complete data set has the advantage that a student may examine data over the entire pH range without excessive time spent in the laboratory. Two students can complete the work described in one three-hour laboratory period using one UV spectrometer.

Theory

Esters, such as the acetyl group in aspirin (acetylsalicylic acid, Figure 1), are subject to hydrolysis. The process may be catalyzed by acid or base or the process may be uncatalyzed ("spontaneous"). The three mechanisms for the hydrolysis of the acetyl group are shown in Schemes I–III.[1] In the acid catalyzed mechanism, if the proton source is hydronium (H_3O^+), the catalysis is termed specific acid catalysis. The source of the proton is from a dissociated acid and the substrate (the ester) is already protonated in the rate-limiting (slow) step of the reaction. Any undissociated acid (if present) does not appear in the rate-limiting step. Specific base catalysis is similar in that the base is hydroxide (HO^-) and the substrate is attacked by hydroxide in the rate-limiting step of the reaction. There are no other bases (such as the conjugate base of an acid) in the rate-limiting step. The spontaneous process shows water acting as the nucleophile attacking a neutral substrate. Each of these process occurs independently of the others and each makes a contribution to the observed rate constant, as shown in eq 1,

$$k_{obs} = k_0 + k_H[H^+] + k_{OH}[^-OH] \qquad (1)$$

where k_0, k_H, and k_{OH} are the rate constants for the spontaneous process, the specific acid catalyzed process, and the specific base catalyzed process, respectively.

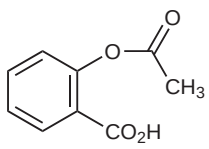
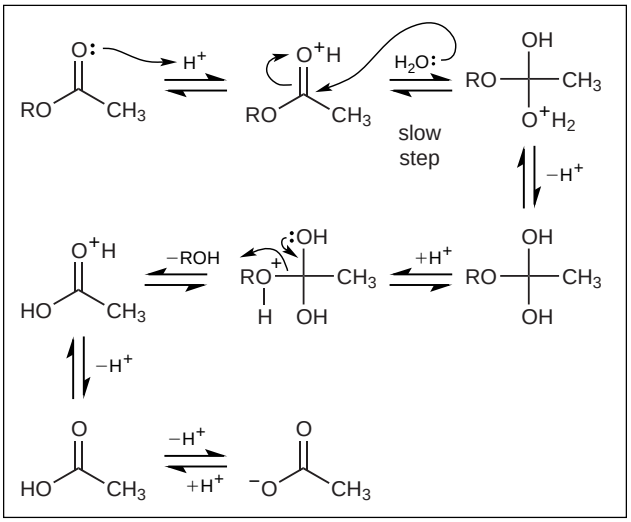
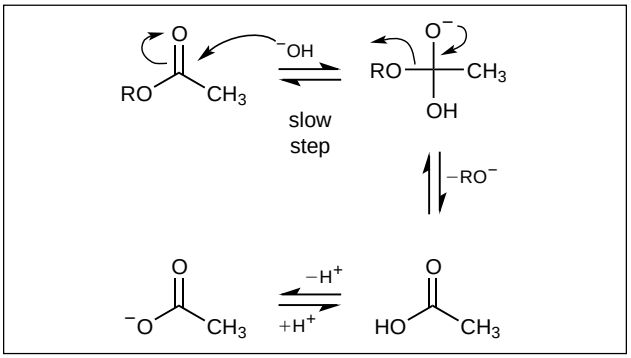


Figure 1. Aspirin.



Scheme I. Specific acid catalyzed hydrolysis.



Scheme II. Specific base catalyzed hydrolysis.

Catalysis also occurs where an undissociated acid is present in the rate-limiting step of the reaction. This catalysis is termed general acid catalysis and the first step of a typical mechanism is shown in Scheme IV. The transfer of the proton to the substrate occurs in the rate-limiting step of the mechanism. Catalysis that involves the conjugate base of an acid in the slow step of the reaction is termed general base catalysis. The first step of a mechanism for this type of catalysis is shown in Scheme V. In this mechanism the conjugate base of the acid is deprotonating water, which is simultaneously attacking the substrate. The process is often called general base assisted nucleophilic attack.

General acid and general base catalysis will contribute a term to the overall observed rate constant for each general acid or base in the reaction. The terms for general acid and general base catalysis are shown in eq 2,

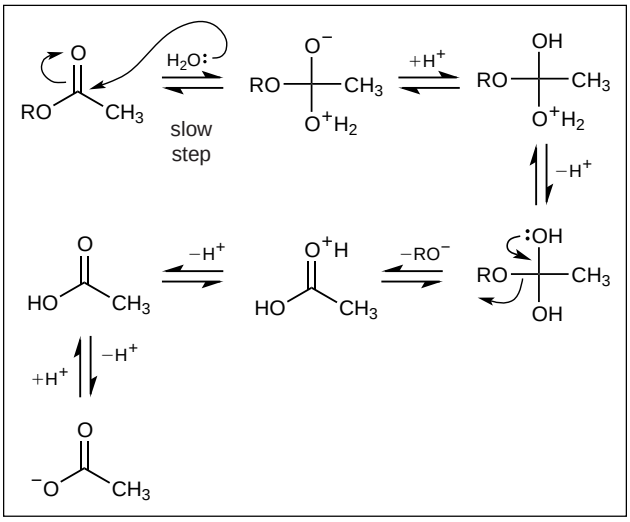
$$k_{obs} = k_0 + k_H[H^+] + k_{OH}[^-OH] + \sum_{HA} k_{HA}[HA] + \sum_{B} k_B[B] \quad (2)$$

where k_{HA} and k_B are the rate constants for each of the general acids and general bases, respectively, and [HA] and [B] are the concentrations of each of the general acids and bases. When no general acids or bases are present, eq 2 reduces to eq 1. Both eqs 1 and 2 contain terms for the hydrogen ion concentration and the hydroxide ion concentration. These terms are, of course, related to the pH of the system. Determination of the observed rate constant over a range of pH values can lead to insights on the mechanism of the reactions.

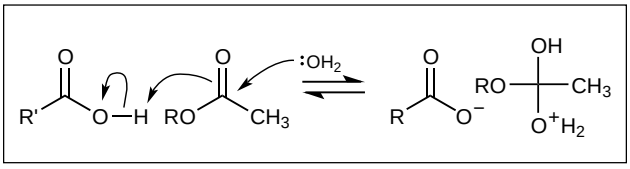
Discussion

The hydrolysis of the acetyl group of aspirin may occur via acid catalysis, base catalysis, or the uncatalyzed process. The carboxylate group of aspirin may be either protonated (CO_2H) or deprotonated (CO_2^-) depending upon the pH of the solution. This leads to six possible reactions for hydrolysis (Scheme VI). The key to understanding the hydrolysis is recognizing that all six process may occur simultaneously and that the observed rate constant is the sum of the rate constants of the individual reactions. In practice, however, it is found that one rate constant dominates the overall process.

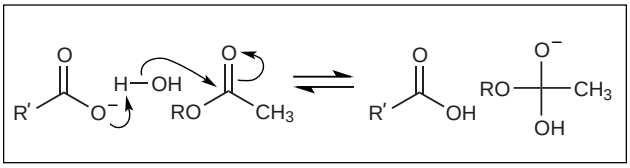
The kinetics are followed by measuring the absorbance of the product formed at 298 nm; the isosbestic point for the salicylic acid–salicylate ion pair. The absorbance of the unhydrolyzed aspirin is essentially zero at this wavelength. The pH of the solutions is maintained by buffers and is measured before the aspirin is added to the reaction mixture. The



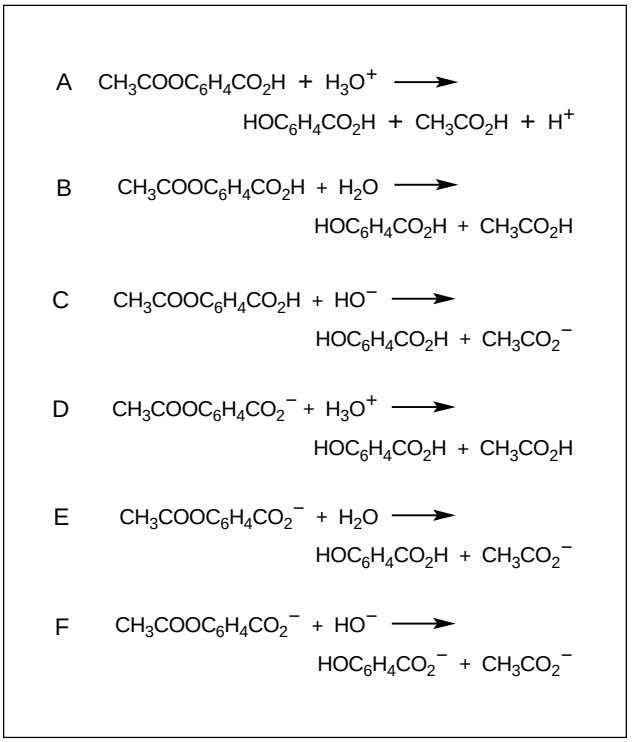
Scheme III. Uncatalyzed hydrolysis.



Scheme IV. General acid catalysis.



Scheme V. General base assisted nucleophilic attack.



Scheme VI. Six possible reactions for hydrolysis:
(A) protonated carboxylate, acid catalyzed hydrolysis;
(B) protonated carboxylate, uncatalyzed hydrolysis;
(C) protonated carboxylate, base catalyzed hydrolysis;
(D) deprotonated carboxylate, acid catalyzed hydrolysis;
(E) deprotonated carboxylate, uncatalyzed hydrolysis; and
(F) deprotonated carboxylate, base catalyzed hydrolysis

ionic strength of the medium was shown not to be a factor in the hydrolysis and the concentration of aspirin is low enough to not affect the pH of the solution *(1)*. The reaction is observed at elevated temperatures (60 °C), otherwise the reaction proceeds too slowly for a normal lab period.

The reaction is first order and eq 3 describes the kinetics,

$$\ln(A_\infty - A_t) = -k_{obs}t \qquad (3)$$

where A_t is the absorbance of the solution at time t, A_∞ is the final absorption of the solution, and k_{obs} is the observed rate constant. A plot of $\ln(A_\infty - A_t)$ versus time provides the rate constant as the negative of the slope of the plot. This protocol leads to a problem in the determination of A_∞; there are logistical difficulties in keeping the reactions at the high temperature for long periods and it is difficult to have the students return the following day to record their values. Thus we have chosen to use a calculated value for A_∞, based on the concentration of aspirin that was used, the known extinction coefficient of the salicylic acid–salicylate ion at 298 nm, and the assumption that all of the aspirin would be hydrolyzed. The calculation of an experimental quantity is not the best approach, but it does give valid results.

A plot of the log of the student-determined first-order rate constants against the pH of the solution is shown in Figure 2. While all of the data points do not fall exactly on the curve, the shape of the curve is obvious and is identical to that determined by Edwards *(1)*. There are four regions on the curve where a different hydrolysis mechanism is occurring. Each of these regions is discussed below.

Region A–B

This region, between pH 0.5 and 2.4, displays a linear relationship between pH and the log(rate constants). At these pH values the acid group of aspirin would be protonated (pK_a = 3.57; ref *1*). The rate is observed to decrease as the pH is raised. From eq 1, this is the behavior expected for specific acid catalysis, thus the mechanism corresponds to specific acid hydrolysis of the acetyl group in the presence of the protonated carboxylate. The spread of data in this region is thought to arise from the inaccuracy in measuring the pH in the strongly acidic solutions.

Region D–E

This region is above pH 8.5 and also displays a linear relationship between pH and the log(rate constant). At these pH values the acid group of aspirin would be completely deprotonated. The rate is observed to increase with an increase in pH. From eq 1, this is the behavior expected for specific base catalysis, thus the mechanism corresponds to specific base hydrolysis of the acetyl group in the presence of the deprotonated carboxylate. The reaction is very fast in this region, especially above pH 9.5, and the difficulty in getting accurate absorbance versus time data accounts for the data spread in this region.

Region C–D

The observed rate of the reaction is independent of pH between pH 4.5 and 8.5. The hydrolysis cannot be occurring by specific base hydrolysis because this process is observed above pH 8.5 and would be less important below that pH. Similarly, the hydrolysis cannot be occurring by the specific acid catalyzed process as this can be seen to be unimportant above pH 2.4. If neither hydroxide or protons are involved in the hydrolysis, then the mechanism for the hydrolysis must involve water as a nucleophile in a "spontaneous" process.

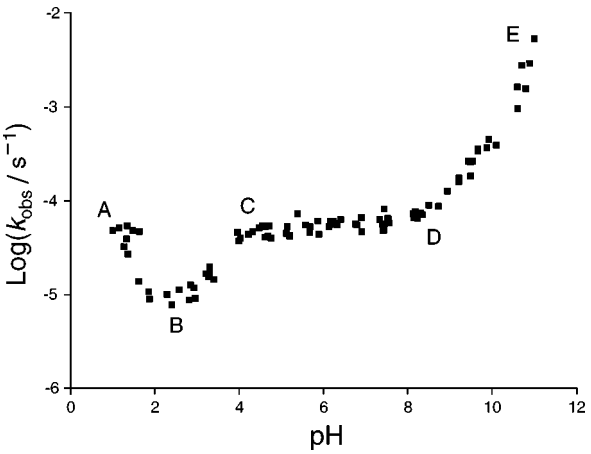
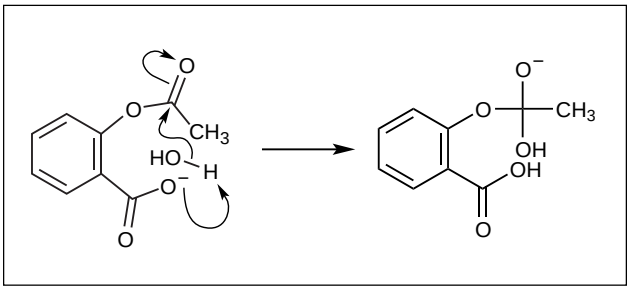


Figure 2. The pH–rate profile for the hydrolysis of aspirin.



Scheme VII. Intramolecular general base catalysis.

When it is reacting on its own, water is a poor nucleophile. This can be understood by examining region A–B of the pH–rate profile, where a strongly acidic solution is required to protonate the carbonyl group of the ester before water can attack. There must be a group assisting the water molecule in becoming a better nucleophile. The assisting group is the acid function of the aspirin molecule. This acid group has a pK_a of 3.57 *(1)* and would be expected at a pH higher than about 4.5 to be present solely as the carboxylate. This group can act as an *intramolecular* general base catalyst by deprotonating a water molecule and allowing the water to act as a stronger nucleophile. The intramolecular catalysis is shown in Scheme VII.

Region B–C

The reaction rate is seen to increase between the minimum rate at pH 2.4 to the plateau beginning at pH 4.5. The

rate of increase is not quite linear in this region, but has more of the shape of a titration curve. The knowledge that the pK_a of aspirin lies within this region provides the clue needed to determine what is occurring. Above pH 2.4, the specific acid catalyzed mechanism becomes less important as the concentration of protons is decreased. At this pH, however, it would be reasonable to expect that a fraction of the aspirin molecules would be present in the carboxylate form. The molecules present as carboxylates would then be able to react via the intramolecular general base assisted nucleophilic-attack mechanism. As the pH of the medium was increased from 2.4 to 4.5, more of the aspirin would be present as carboxylate and the observed rate of reaction would increase as the intramolecular general base mechanism became more important. Above pH 4.5, all of the aspirin would be present as salicylate and the observed rate due to intramolecular catalysis would not be expected to change with a change in pH.

Of the reactions proposed above, two of the possibilities, acid catalyzed hydrolysis with a deprotonated carboxylate and base catalyzed hydrolysis with a protonated carboxylate, are unlikely given the pH behavior of aspirin. The final possibility, a "spontaneous" reaction of water with the protonated carboxylate *is* possible, because the acid group can act as an intramolecular general acid. Although this mechanism can be proposed, there is no evidence from the pH–rate profile that it becomes the dominant mechanism for hydrolysis. The possibility that the buffer components are acting as general acid or general base catalysts has be discounted by Edwards *(5)*.

Summary

The pH–rate profile for the hydrolysis of aspirin may be understood by understanding the pH behavior of the aspirin molecule and the hydrolysis mechanisms available at different pH values.[2] This experiment was first tried in the fall of 1995 and has been successful from the beginning. The laboratory reports submitted by the students show their ability to understand the meaning of the pH–rate profile and the reasons for the changes in the mechanism. Acid, base, and intramolecular catalysis form a large part of the lecture topics and this experiment is an excellent practical exercise reinforcing the concepts taught in the lecture.

Hazards

Some of the buffer components are caustic and toxic; however, the preparation of the buffer components is handled by a technician. The students prepare their own buffer mixtures from the components and standard laboratory safety practices (safety glasses, gloves, and lab coats) should suffice for this experiment.

Acknowledgments

We thank the students and teaching assistants of Chemistry 337, classes of 1995 through 2001, for their input and suggestions for this experiment. The Chemistry 337 class of 2001 supplied the data shown in Figure 2. We thank the referees for their constructive comments.

[w]Supplemental Material

Instructions for the students and notes for the instructor are available in this issue of *JCE Online*.

Notes

1. The position of the acetic acid–acetate equilibrium in Schemes I and III is pH dependent. In Scheme II, the medium is basic enough (pH > 8) to completely deprotonate the acetic acid formed. The removal of the acetic acid from the reaction makes the basic hydrolysis of esters irreversible.

2. A figure from Edwards' paper (ref *1,* page 732, figure 8) demonstrates how the pH–rate profiles of the different types of catalysis can be added to give a complete picture of the catalysis over the full pH range.

Literature Cited

1. Edwards, L. J. *Trans. Faraday Soc.* **1950,** *46,* 723. This paper is an excellent example of what a research report should be. Although the intramolecular reaction was not proposed in this paper, all other issues relating to the hydrolysis of aspirin are completely covered.
2. For examples, see; Garrett, E. R. *J. Am. Chem. Soc.* **1957,** *79,* 3401 or Fersht, A. R.; Kirby, A. J. *J. Am. Chem. Soc.* **1967,** *89,* 4857. The latter paper describes the work that confirmed the existence of the mechanism of intramolecular general base catalysis by the carboxylate group.
3. (a) Correia, L. C.; Bocewicz, A. C.; Esteves, S. A.; Pontes, M. G.; Versieux, L. M.; Teixeira, S. M. R.; Santoro, M. M.; Bemquerer, M. P. *J. Chem. Educ.* **2001,** *78,* 1535. (b) Khan, M. N. *J. Chem. Educ.* **1998,** *75,* 632. (c) Head, M. B.; Mistry, K. S.; Ridings, B. J.; Smith, C. A.; Parker, M. J. *J. Chem. Educ.* **1995,** *72,* 184. (d) Potts, R. A.; Schaller, R. A. *J. Chem. Educ.* **1993,** *70,* 421. (e) Adams K. R.; Meyers, M. B. *J. Chem. Educ.* **1985,** *62,* 86. (f) Lombardo, A. *J. Chem. Educ.* **1982,** *59,* 887. (g) Bulmer, R. S.; Senogles, E.; Thomas, R. A. *J. Chem. Educ.* **1981,** *58,* 738. (g) Blackman, D. *J. Chem. Educ.* **1978,** *55,* 722. (h) Rosenthal, D.; Arnold, D. *J. Chem. Educ.* **1977,** *54,* 323. (i) Leisten, J. A. *J. Chem. Educ.* **1961**, *38,* 132.
4. (a) Klausen, J.; Meier, M. A.; Schwarzenbach, R. P. *J. Chem. Educ.* **1997,** *74,* 1440. (b) Breslow, R. *J. Chem. Educ.* **1990,** *67,* 228.
5. Edwards, L. J. *Trans. Faraday Soc.* **1950,** *46,* 729.