The Hammett Equation: Probing the Mechanism of Aromatic Semicarbazone Formation

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The Hammett equation and its applications are covered in a single-semester, third-year organic chemistry course at this university. Hammett studies provide insight into a particular reaction mechanism by probing structure-reactivity relationships (1). However, many organic reactions are impractical for demonstrating the Hammett equation in an undergraduate environment (2, 3). Both the time constraints of the laboratory period and the requirement for reproducible data with sufficient accuracy to convey the underlying chemical theory eliminate many potential reactions for study. Moreover, collection and analysis of kinetic data often requires skills possessed by the average upper-level undergraduate. Herein we report a cooperative kinetics experiment that meets these criteria while providing students practical insight into the meaning and interpretation of the Hammett equation.

The reaction studied is the formation of an aromatic semicarbazone from semicarbazide and a corresponding meta- or para-substituted benzaldehyde (Scheme I). To our knowledge, this is a unique undergraduate laboratory where a Hammett plot is developed utilizing rate constants determined by UV-vis spectroscopy. Marrs recently reported the measurement of UV-vis absorption spectra to obtain Hammett plots for ionization of para-substituted phenols (4). Other experiments published in this Journal have focused on constructing Hammett plots via a number of other practical techniques, including $^{13}$C NMR spectroscopy (2), $^1$H NMR spectroscopy (3, 5), and acid–base titration (6, 7). Reviews by Jaffé (8) and more recently by Hansch et al. (9) outline the importance of the Hammett equation in studying reactivity of organic molecules,

$$\log \frac{k_X}{k_H} = \rho \sigma_X$$

where $k_X$ is the rate constant for the substituted benzaldehyde, $k_H$ is the rate constant for the unsubstituted benzaldehyde, $\rho$ is the reaction constant, and $\sigma_X$ is the substituent constant. Theory underlying this relationship is described in the Supplemental Material.

**Experimental Overview and Results**

The mechanism of aromatic semicarbazone formation from semicarbazide and benzaldehyde has been thoroughly investigated by Jencks et al. (10–12) and involves two potential rate-determining steps (defined as rds, Scheme II): The
At first consists of nucleophilic addition to form a carbinolamine intermediate (rdsa) and precedes the second, which involves dehydroxylation (rdsb). One of these steps is rate-determining as each involves heavy-atom bond formation or cleavage. All other mechanistic steps involve faster (proton transfer) events with every reaction step reversible. The primary goal for students is to experimentally deduce which reaction step is rate-determining under strongly acidic conditions.

The instructor prepares stock solutions of meta- and para-substituted benzaldehydes (~7 mM, 80%:20% v/v water: ethanol) and semicarbazide hydrochloride (0.4 M, water). Students prepare reactant solutions from these stock solutions by appropriate dilutions. The semicarbazide hydrochloride reactant solution is made up using 0.1 M HCl such that the pH during a kinetic run is 1.7. Semicarbazone formation is monitored by the characteristic absorbance increase between 280–320 nm after mixing the reactant solutions. As second-order kinetics are followed at pH 1.7 (10), semicarbazide is present in > 1000-fold excess to obtain pseudo first-order conditions (13) and a simplified rate law:

$$\text{rate} = \frac{d[\text{benzaldehyde}]}{dt} = k_{\text{obs}}[\text{benzaldehyde}]$$  \hspace{1cm} (2)

Absorbance versus time kinetic data are subsequently fitted to eq 3 using appropriate software (e.g., GraFit; ref 14),

$$A_t = (A_0 - A_{\infty})e^{-k_{\text{obs}}t} + A_{\infty}$$  \hspace{1cm} (3)

where $k_{\text{obs}}$ is the observed pseudo first-order rate constant, $A_t$ is the absorbance at time $t$, $A_0$ represents the constant absorbance at the end of the reaction ($t = \infty$), and $A_{\infty}$ is the absorbance at the reaction inception ($t = 0$).

Each student is assigned either the parent benzaldehyde or one of nine meta- or para-substituted benzaldehyde derivatives. Kinetic runs are performed in duplicate or triplicate and all calculated rate constants submitted to the instructor for tabulation and distribution to the entire class. The instructor obtains kinetic data for the $p$-NO$_2$ and $p$-OCH$_3$ benzaldehyde derivatives\(^1\) so that a twelve-point Hammett plot is constructed.

A good linear relationship ($r^2 = 0.983$) is observed between average experimental rate constants and literature $\sigma_X$ values (9) (Figure 1).\(^2\) The slope of this Hammett plot gives $\rho = +0.90$, in excellent agreement with the literature value of +0.91 (11). The slowest student kinetic run (for $p$-CH$_3$) takes 20 minutes and the fastest (for $m$-NO$_2$) 5 minutes, which is extremely convenient from a practical perspective. A comparison of $\rho = +0.90$ for semicarbazone formation with $\rho = +1.00$ for benzoic acid dissociations indicates the magnitude of electronic effects are similar for two very different systems.

The positive value of $\rho$ is consistent with the first step (Scheme II, rdsa) being relatively slow and rate-determining under strongly acidic conditions. At pH 1.7 a significant quantity of unreactive protonated semicarbazide exists in solution ($pK_aH_2NC(O)NH\text{H}_3^+ = 3.82$) (15). The effective concentration of nucleophilic semicarbazide available for reaction is therefore significantly attenuated.\(^3\) Attack at the carbonyl carbon by the semicarbazide amino group occurs faster with an electron-withdrawing group meta- or para- to the aldehyde functionality. This observation involves ground-state destabilization, whereby such groups (e.g., $m$-NO$_2$, $p$-CN) pull electron density away from the carbonyl carbon, increasing its positive character and activating it further as an electrophile. Overall, electron-withdrawing groups lower the activation energy associated with rdsa and rate acceleration is seen for substituents with more positive $\sigma_X$ values, leading to $\rho = +0.90$. At pH 1.7 the dehydration step (Scheme II, rdsb) is relatively fast. The carbinolamine hydroxy group is converted to its conjugate acid, allowing H$_2$O to act as a good leaving-group and depart in a dissociative-type mechanism.

**Laboratory Report**

Students are instructed to submit a formal laboratory report including a detailed reaction mechanism, Hammett plot, and interpretation of all results. Reports generally reflect a conceptual understanding of the Hammett equation and the electronic effects imparted by various substituent groups. Students are additionally encouraged to use their Hammett plot for predictive purposes. Rate constants or $\sigma_X$ values can be determined for a system where the $\rho$ value and one of the two variables are defined. The rate constant for semicarbazone formation from $p$-hydroxybenzaldehyde is measured by the instructor and the class asked to calculate $\sigma_X$ for the $p$-hydroxy substituent. Comparison with the literature value ($\sigma_{p-OH} = -0.37$; ref 9) gives an indication as to the accuracy of the Hammett plot obtained. The rate constant for semicarbazone formation from 3,5-dimethoxybenzaldehyde can also be predicted from the plot by interpolation, assuming that the electron-withdrawing effect of each $m$-OCH$_3$ substituent is additive. As 3,5-dimethoxybenzaldehyde is commercially available,\(^4\) the true rate constant can be measured and compared with the forecasted value.

An essential extension of the post-laboratory report deals with the concept of a nonlinear Hammet plot. This emphasizes that $\rho$ values provide information about the rate-determining step in a multistep mechanism. Students are challenged to consider the same reaction carried out at pH 6.5 rather than under strongly acidic conditions, by con-

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**Figure 1. Student Hammett plot for semicarbazone formation where nucleophilic addition is rate-determining, pH = 1.7.**
sulting a research article (16). A concave-downwards Hammett plot is observed (Figure 2), indicative of a change in rate-determining step that results from differing electronic contributions of the substituents (17). With electron-donating substituents, the dehydration step (Scheme II, rds b) is still relatively fast with nucleophilic addition (rds a) remaining rate-determining (p = positive). However, electron-withdrawing groups speed up nucleophilic addition but slow down dehydration, which is now rate-determining. The dehydration step involves build up of positive charge closer to the aromatic ring as the iminium ion generated is represented by two resonance forms (Scheme II). Therefore, rds b will be slowed by strong electron-withdrawing groups and p = negative on the right-hand side of the Hammett plot.

The collaborative nature of this experiment makes it ideally suited to a large upper-level mechanistic laboratory. Kinetic runs are undertaken on a desirable timescale permitting the acquisition of data for many benzaldehyde derivatives. Students appreciate that linear (and nonlinear) Hammett plots provide much insight into organic reactivity and that a reaction's rate-determining step can change if experimental conditions are altered.

Hazards

The benzaldehyde reactants used in this experiment are skin irritants and semicarbazide hydrochloride is toxic; however, all stock solutions are prepared by the instructor. Ethanol is a flammable solvent and hydrochloric acid can cause severe burns.

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*Supplemental Material*

Theory underlying the Hammett equation, instructions for the students, and notes for the instructor are available in this issue of *JCE Online*.

Notes

1. Students have invariably encountered difficulty in accurately measuring k_{obs} for the p-NO_2 derivative (half-life = 13 s). The instructor measures and takes an average of five kinetic runs for this compound. The half-life for the 4-methoxybenzaldehyde reaction is 2.1 minutes (kinetic run time = 30 minutes).

2. The data in Figure 1 were obtained by 72 students during six, three-hour laboratory sessions (spread over two weeks) using three UV–vis spectrometers. All rate constants were measured at room temperature. Straightforward protocol modification allows a six-point Hammett plot to be generated in a single three-hour session (12 students using three spectrometers). Much experimental flexibility exists depending on equipment and curricular time available.

3. Note that nucleophilic semicarbazide is in rapid equilib-