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Deducing Reaction Mechanism: A Guide for Students, Researchers, and Instructors

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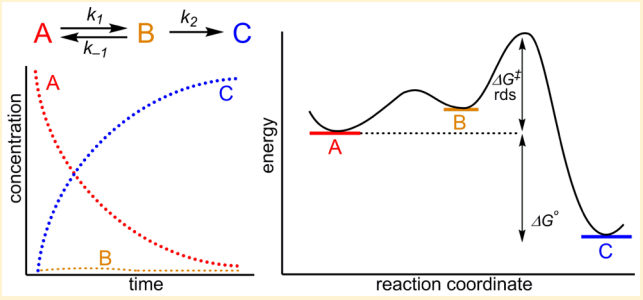
Supporting Information

ABSTRACT: An introductory guide to deducing the mechanism of chemical reactions is presented. Following a typical workflow for probing reaction mechanism, the guide introduces a wide range of kinetic and mechanistic tools. In addition to serving as a broad introduction to mechanistic analysis for students and researchers, the guide has also been used by instructors to provide the organizational structure for an upper-level course on organic and inorganic reaction mechanism. After providing students with the tools of mechanistic study, student-led discussions of case studies and an independent proposal project provide preparation for understanding the mechanism of new reactions encountered in independent research.



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INTRODUCTION

Mechanistic understanding of chemical reactions drives research and guides teaching of reactivity in chemistry. Upper-level physical organic or organometallic chemistry courses often discuss reaction mechanism in detail, in the context of prototypical example reactions. Based on the equal importance of understanding mechanism in the classroom and in the research laboratory, a pedagogical approach that focuses on empowering students with the tools needed to interrogate reactions was envisioned.

This contribution provides an accessible, practical guide for students and researchers embarking on a mechanistic study. This guide can be a useful tool for (a) advanced undergraduate and first-year graduate students learning kinetics, physical organic chemistry, or organometallic chemistry; (b) researchers who are new to mechanistic study; and (c) instructors interested in a student-centered approach to teaching reaction mechanism that focuses on case studies. While not a replacement for the numerous excellent textbooks on chemical kinetics[1−4] and physical organic chemistry,[5−8] the guide introduces a curated collection of experimental techniques supported by leading references and literature examples. An interdisciplinary upper-level course structured around the guide involves a student-driven approach to solving puzzles of chemical reactivity. After introducing the tools of mechanistic inquiry in a series of lectures (supported by group problem solving sessions), class time is devoted to student-led discussion of case studies from the literature, culminating in a research project in which students craft their own proposals for a mechanistic study.

GUIDE TO DEDUCING REACTION MECHANISM

Step 0. Know the Identity of Reactants and Products

The important task of characterizing the reactants and products involved in a reaction is often overlooked in the hasty pursuit of knowledge. Reactants should be well-defined and pure, and the products should be fully characterized. Knowledge of the starting and end points of a chemical transformation is required in order to propose plausible reaction pathways. Product characterization can also give early clues, such as whether a reaction proceeds with retention of stereochemistry.

Step 1. Ensure That the Reaction Is as Clean as Possible

A reaction of interest is much more easily studied if the transformation proceeds to the desired product in high yield. Unfortunately, reactions do not always proceed cleanly; time spent finding optimal reaction conditions is often worth the effort. Mechanistic information on a reaction that is ill-defined or proceeds to multiple products should be interpreted with caution. Techniques such as initial rate methods or ensemble-based kinetic models may help simplify the situation.[9−11]

Step 2. Consider Various Mechanistic Possibilities

Sketch mechanistic hypotheses, building reaction pathways from a series of elementary steps. Use logical electron pushing guidelines to support your reaction pathways.[1−4,12] Creativity and open-mindedness are often rewarded in this process. It can be helpful to prioritize the various possible mechanisms based

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Table 1. Differential Equations and Integrated Rate Laws for Use in Graphical Kinetic Analysis

Order	Differential Equation	Integrated Expression	Half-Life Expression	Graph Drawn (Linear Fit)
0	$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = k[\mathrm{A}]^0 = k$	$[\mathrm{A}]_t = [\mathrm{A}]_0 - kt$	$t_{1/2} = \frac{[\mathrm{A}]_0}{2k}$	$[\mathrm{A}]_t$ vs t (slope $= -k$)
1	$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = k[\mathrm{A}]$	$\ln[\mathrm{A}]_t = \ln[\mathrm{A}]_0 - kt$	$t_{1/2} = \frac{\ln 2}{k}$	$\ln[\mathrm{A}]_t$ vs t (slope $= -k$)
2	$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = k[\mathrm{A}]^2$	$\frac{1}{[\mathrm{A}]_t} = \frac{1}{[\mathrm{A}]_0} + kt$	$t_{1/2} = \frac{1}{k[\mathrm{A}]_0}$	$\frac{1}{[\mathrm{A}]_t}$ vs t (slope $= +k$)
1/2	$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = k[\mathrm{A}]^{1/2}$	$[\mathrm{A}]_t^{1/2} = [\mathrm{A}]_0^{1/2} - \frac{1}{2}kt$	$t_{1/2} = \frac{(2-\sqrt{2})[\mathrm{A}]_0^{1/2}}{k}$	$[\mathrm{A}]_t^{1/2}$ vs t $\left(\text{slope} = -\frac{1}{2}k\right)$

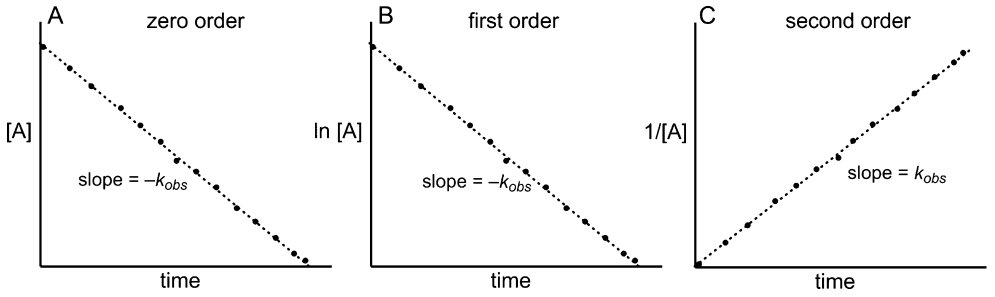

Figure 1. Graphical analysis methods illustrating the expected linear fit for zero-order (A), first-order (B), and second-order (C) reactions. Reaction data can be plotted each way to determine which order provides the most accurate linear fit.

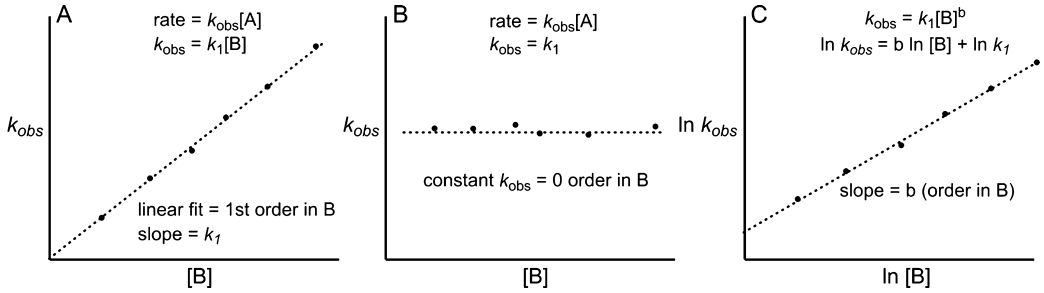

Figure 2. Graphical analysis for determination of order in [B] and rate constant k_1. A linear dependence is observed if the reaction is first order in [B] (A) while no dependence is observed if the reaction is zero order in [B] (B). A logarithmic treatment (C) should result in a linear correlation in which the slope reveals the order in [B]. In all cases, [A] is held constant and 10-fold less than [B].

on precedent, but the common pitfall of assuming that a "likely" mechanism is operating should be avoided (this assumption clouds judgment when designing experiments to probe mechanism as described below). Electron counting conventions (octet and 18-electron rules) can provide some chemical intuition regarding the plausibility of intermediates.[13,14] Predicting the "rate-determining step" (rds, see below) can dramatically simplify the situation, based on assumptions (e.g., proton transfer and solvation are fast). Draw each pathway as a series of elementary reactions, and consider which steps are likely to be reversible.

Step 3. Obtain the Empirical Rate Law

Experimental techniques can *differentiate* potential mechanisms. This can involve "disproving" one mechanistic possibility or obtaining evidence in support of another. In favorable circumstances, a particular reaction mechanism consistent with all assembled evidence will emerge as the most likely chemical pathway. It is often stated that a mechanism cannot be conclusively proven. This maxim stemming from the philosophy of Karl Popper,[15,16] while controversial,[17−21] does serve as motivation to analyze a reaction in sufficient detail to build confidence in a particular mechanism. The following sections introduce various techniques of mechanistic interrogation, organized roughly in the order in which one might carry out a series of experiments.

Kinetic Analysis of Simple Systems. Kinetic analysis is the study of reaction rate by monitoring changes in the concentration of reactants. Mathematical and graphical analysis of reaction data can provide (a) the order in each reagent and (b) the rate constant of the reaction. Classical kinetic analysis of solution[22] reactions involves a *two-step process* for determining the order of reagents—and thus the rate law.[23−27] Note: Reactions involving a single step and reactions with a rate-determining (slowest) first step are good candidates for the two-step process of kinetic analysis.

Classical kinetic analysis is performed under *pseudo-first-order conditions* (>10-fold excess of nonlimiting reagent(s)), so the concentration of excess reagent(s) remains *effectively constant* during the reaction. A bimolecular elementary reaction (eq 1) will have the rate law in eq 2, which simplifies to the form of eq 3 under pseudo-first-order conditions.

$$\mathrm{A} + \mathrm{B} \xrightarrow{k_1} \mathrm{P} \tag{1}$$

$$\text{rate} = k_1[\mathrm{A}][\mathrm{B}] \tag{2}$$

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$$\text{rate} = k_{obs}[A] \quad (3)$$

where $k_{obs} = k_1[B]$, when $[B] > 10[A]$.

In the first step of a two-step kinetic analysis, the order in A and a value of the observed pseudo-first-order rate constant (k_{obs}) are obtained according to Table 1 by fitting the concentration decay profile over time. The data can be plotted in different ways, and the method that yields the best linear fit suggests the order (Figure 1). Note: Linear fits should be visually inspected in addition to noting the correlation coefficient (r^2); good fits will show random deviation, so beware of systematic deviations (i.e., curvature; see Supporting Information).

In the second step, the order of the other reagent(s) and the reaction rate constant (k_1) are determined based on how k_{obs} changes as a function of the concentration of another reagent of interest ($[B] > 10[A]$; [A] = constant). A plot of k_{obs} vs [B] will be linear if the reaction is first order in B (Figure 2A), with slope equal to the second-order rate constant, k_1 ($M^{-1}\cdot s^{-1}$). A "log–log" plot of ln k_{obs} vs ln [B] (or log k_{obs} vs log [B]) should be linear, with slope equal to the order in B (Figure 2C).

Data quality will depend on various factors, including how cleanly the reaction proceeds and the number of data points collected during the reaction (time resolution). Concentration changes should be monitored beyond 3 half-lives, because first- and second-order reactions are hard to distinguish with less data and because time courses will appear linear over very short time scales. In contrast, *the method of initial rates* uses *only* the data from early times, approximated to a linear fit. Initial rate measurements are popular because they are quick and require no data manipulation. A true rate constant is *not* obtained, and the valuable information contained in the later parts of the decay is lost. Nonetheless, measuring the initial rate while varying the initial concentration of one reagent (while keeping the initial concentration of the other reagent constant) enables analysis according to Figure 2 (plotting initial rate instead of k_{obs}).

Kinetic Analysis of Chemical Equilibrium. Many reactions proceed to an equilibrium mixture of products that is dictated by thermodynamic parameters. When a reaction establishes equilibrium slowly relative to the experimental technique being utilized, the kinetics of approach to equilibrium are similar to the simple systems described above. The concentration of A does not go to zero, however, so the data can be fit using least-squares analysis or using equations that take into account the final equilibrium concentration of A.[1,28,29] Reactions that undergo rapid equilibration can be studied using a powerful array of NMR techniques that include temperature-dependent line broadening studies and magnetization transfer experiments.[30]

Kinetic Analysis of Complex Systems. Most chemical reactions involve multiple steps, a situation most clearly indicated by the direct observation of an intermediate.[31] If an intermediate is too reactive to be observed, its presence can also be established by kinetic analysis.[32,33] Complex systems are difficult to treat with simple graphical methods (and are often best analyzed by least-squares analysis), but there are limiting regimes where approximations render graphical methods useful.

The *steady-state approximation* is most commonly employed for two-step reactions in which the first step is reversible (eq 4).[1]

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} I \xrightarrow{k_2} P \quad (4)$$

The steady-state approximation assumes that I is highly reactive: [I] is *small* and *constant*, and $k_1 \ll k_2 + k_{-1}$. This leads to the rate law of eqs 5 and 6 (see Supporting Information for additional cases). Note: The rate law is in a familiar form that can be assessed graphically as described above.

$$\text{rate} = \frac{d[P]}{dt} = k_{obs}[A] \quad (5)$$

$$k_{obs} = \frac{k_1 k_2}{k_{-1} + k_2} \quad (6)$$

The *pre-equilibrium approximation* is also commonly used to treat multistep systems. The chemical situation of eq 4 is again considered, but the pre-equilibrium approximation *does not require* a small, unchanging [I]. The pre-equilibrium approximation assumes that A and I interconvert rapidly and maintain equilibrium (eq 7), resulting in the rate law of eq 8 (where $k_2 \ll k_1 + k_{-1}$). Mass balance (eq 9) can taken into account to monitor the reaction using [P] or to solve an integrated rate law.

$$\frac{k_1}{k_{-1}} = \frac{[I]}{[A]} \quad (7)$$

$$\text{rate} = \frac{d[P]}{dt} = K_{eq} k_2 [A] \quad (8)$$

$$[A] = [A]_0 - [I] - [P] \quad (9)$$

Steady-state and pre-equilibrium approximations are best used when a reaction *appears* first order, but is suspected to be more complex. In cases with multiple reactants, "saturation kinetics" offers another hint that a hidden equilibrium is present. As discussed in the Supporting Information, saturation occurs when the reaction order changes from 1 to 0 with increasing reactant concentration.

Kinetic Analysis of Catalytic Reactions. Catalytic reactions are unusual at first glance because the catalyst is not consumed during the reaction (Figure 3), but the treatment is not fundamentally different from that for other reactions. A review on mechanistic studies of homogeneous catalytic reactions is available.[34]

Catalytic reactions are often studied using the method of initial rates.[35] Catalytic performance is also compared using turnover number (TON), the moles of product divided by the

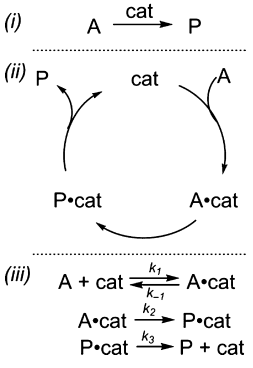

Figure 3. Different schematic representations of a catalytic reaction.

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moles of catalyst; and turnover frequency (TOF), the turnover number divided by a unit of time. Be careful not to plot TON or TOF vs [catalyst], as TON and TOF intrinsically depend on [catalyst]. Spectroscopic monitoring can also identify the "resting state" of a catalytic cycle: the species observed in highest concentration *during active turnover*.[36]

The Michaelis–Menten kinetic treatment,[37] developed for enzyme catalysis, applies a version of the steady-state approximation (eq 10). It is commonly used in biology, but applicable to any chemical system.

$$\text{rate} = \frac{V_{\max}[\text{A}]}{K_{\text{M}} + [\text{A}]} \tag{10}$$

where $V_{\max} = k_2[\text{cat}]_0$; $K_{\text{M}} = \frac{k_{-1} + k_2}{k_1}$; k_2 is the rate-determining step.

An additional assumption, beyond typical steady-state conditions, is introduced to account for the fact that the concentration of catalyst during the reaction is not readily measurable. The relationship $[\text{cat}]_0 = [\text{cat}]_t + [\text{A·cat}]$ provides a means of using the known initial catalyst loading, $[\text{cat}]_0$, in eq 10. This is illustrated by comparing the original steady-state approximation (derived from eq 11) and the Michaelis–Menten treatment (eq 12), which leads to the [A] term appearing in the denominator of eq 10.

$$\text{rate} = k_1[\text{cat}][\text{A}] - k_{-1}[\text{A·cat}] - k_2[\text{A·cat}] = 0 \tag{11}$$

$$\text{rate} = k_1([\text{cat}]_0 + [\text{A·cat}])[A] - k_{-1}[\text{A·cat}] - k_2[\text{A·cat}] = 0 \tag{12}$$

Figure 4 shows the graphical method commonly used, which is typically composed of several initial rate data points, and the kinetic information that can be extracted from the resulting plot.

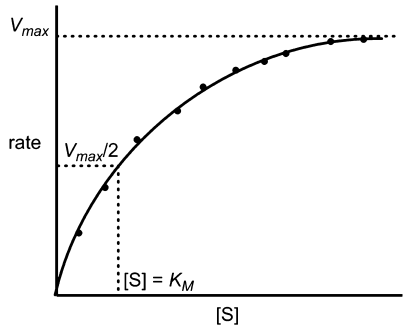

Figure 4. Plot of rate vs substrate concentration, [S], used in Michaelis–Menten and reaction progress kinetic analysis.

Reaction progress kinetic analysis (RPKA) uses *in situ* kinetic analysis to provide more accurate and data-rich plots of rate vs [S].[38−41] By tracking the disappearance of [S] in real time, plots that were made with 5−10 experiments in Figure 4 can be obtained in a single experiment. Beyond minimizing the number of experiments, RPKA can provide information on catalyst stability and reagent order by altering reaction conditions to maintain either "same excess" or "different excess" between reagents and assessing the resulting graphs for "overlay". RPKA is particularly useful when trying to maximize kinetic information with minimal material (and minimal number of experiments), and when faced with complex and/or poorly defined catalytic reactions.

Kinetic Analysis by Least-Squares Fitting Software. Exact solutions to even the most complex kinetic situations can be obtained on modern personal computers using one of several available software packages that provide intuitive graphical user interfaces for fitting experimental data. One example is Copasi,[42] a free program originally designed for biochemical kinetics that is flexible enough to handle any kinetic situation. A common usage starts with inputting a data set that follows the concentration of one or more reagents over time. Then, the user can generate the rate law for a proposed mechanism, and the software will fit the data using least-squares analysis in order to obtain a solution for the various rate constants. If the data cannot be fit precisely, the proposed rate law might be incorrect, and the user can try other reaction sequences that would lead to different rate laws. An excellent fit supports the rate law, providing the order in reagents and rate constants.

Least-squares fitting software has several advantages over classical kinetics: pseudo-first-order conditions (and large reagent excess) can be avoided, and no approximations are required, for example. A deep understanding of kinetic analysis, however, is still valuable: additional experiments varying the concentrations of reagents should all fit the same overall rate law, for example. Teaching classical pseudo-first-order kinetics before introducing more complexity and modern methods is often fruitful.

Step 4. Establish the Nature of the Transition State

When considering how a reaction proceeds, the molecular arrangements of the transition state (TS) can provide a great deal of insight. Mechanistic tools can provide information on whether bonds are breaking or being formed, how ordered the system is, how much (and what kind of) charge is building up, whether a change in hybridization is occurring, and more. Sometimes this sort of information is even more important than reaction rates or reagent orders, but many of the techniques described below build on the kinetic analysis introduced above.

Reaction Coordinate Diagrams. To draw a reaction coordinate diagram (Figure 5), start with the thermodynamic features: what are the relative free energies ($\Delta G°$) of reactants, products, and any observed intermediates? Each stable species is depicted as an energy minimum ("well"), and transition states are depicted as barriers ($\Delta G^{‡}$). If any species are in rapid equilibrium, this should be reflected with close energy spacing between these species and a low barrier.

The "rate-determining step" (rds) is conveniently illustrated in reaction coordinate diagrams, although this concept can be a source of confusion in complex reactions.[36,43,44] The rate-determining step (or steps) features the highest barrier ($\Delta G^{‡}$) and is thus the primary determinant of the overall reaction rate. In a reaction coordinate diagram, the rds can be identified based on the relative energy of the various stable species and on the relative barrier heights. For reactions that feature high-energy intermediates, all steps from the reactant to the highest barrier will contribute to the rds (Figure 5C). In some unusual cases (e.g., a very low energy intermediate, Figure 5D), the rds (highest barrier) is not the highest energy point on the overall reaction coordinate. Steps that occur after the rds do not figure in the rate law. The rds can be determined using kinetic analysis or based on the "resting state": the intermediate species of

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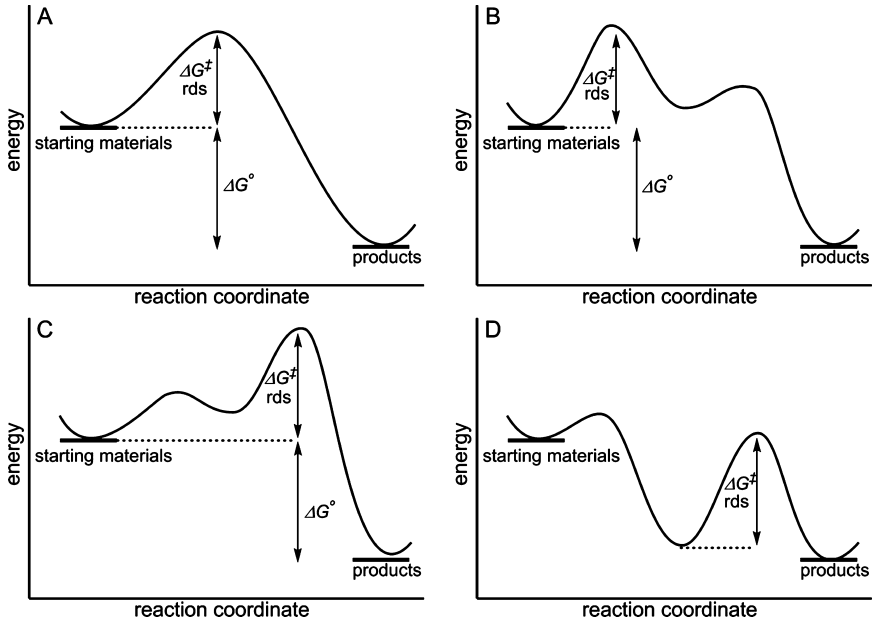

Figure 5. Various reaction coordinate diagrams for one- and two-step reactions. The rds is noted in each case; note that in C the rds is a composite of two steps.

highest concentration during a reaction will be dictated by the rds.

Transition-State Theory and Temperature Dependence. Transition-state theory (TST) introduces methods for learning about the structure of the transition state.[45−47] TST is ideal for elementary (single-step) reactions and can become muddled if multiple steps contribute to the rate law. TST tells us about (A) enthalpy of activation ($\Delta H^{\ddagger}$), which reflects how much bond breaking and bond forming is occurring in the transition state; and (B) entropy of activation ($\Delta S^{\ddagger}$), which reflects whether the transition state is more or less ordered than the ground state.

Although this section will focus on more quantitative aspects of TST, there are some qualitative aspects, such as the Hammond postulate: the transition state of a single-step reaction will be closer in energy (and similar in structure) to the higher-energy species.[48−50] That is, exothermic reactions will have "early" transition states that look like reactants; and endothermic reactions will have "late" transition states that look like products. Similarly, Jencks plots map out possible reaction pathways to predict transition-state structures.[51]

Quantitative activation parameters can be derived from the Eyring and Arrhenius equations, both of which rely on measuring reaction rates over as wide a temperature range as possible. For single-step reactions, the Eyring equation can be applied (eq 13, where the transmission coefficient, κ, is generally taken as 1).[7] Linearization provides eq 14; Figure 6 illustrates how the enthalpy of activation ($\Delta H^{\ddagger}$) and entropy of activation ($\Delta S^{\ddagger}$) can be obtained graphically.

$$k = \frac{\kappa k_B T}{h} e^{-\Delta G^{\ddagger}/RT} \tag{13}$$

$$\ln\left(\frac{k}{T}\right) = -\frac{\Delta H^{\ddagger}}{RT} + \ln\left(\frac{k_B}{h}\right) + \frac{\Delta S^{\ddagger}}{R} \tag{14}$$

When multiple elementary steps are included in the reaction, eq 15 can be used to generate an Arrhenius plot ($\ln k$ vs $1/T$) which is applicable to both single and multistep reactions. The

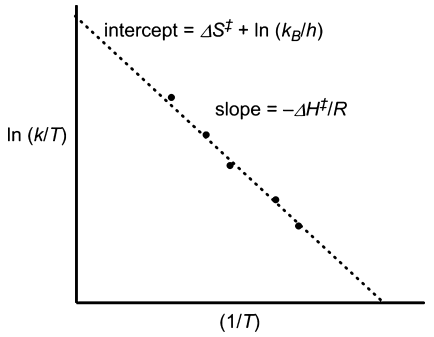

Figure 6. Eyring plot correlating rate constant and temperature, illustrating how activation parameters can be obtained.

activation energy, E_a (similar to $\Delta H^{\ddagger}$), can be obtained from the slope, and an estimation of $\Delta S^{\ddagger}$ can be obtained from the intercept: $\ln A$.[52] Variable-temperature NMR techniques based on temperature-dependent line broadness can also provide activation parameters according to the Arrhenius equation.[30]

$$\ln k = \ln A - \frac{E_a}{RT} \tag{15}$$

Interpretation of activation parameters provides information on the nature of the transition state. The magnitude of $\Delta H^{\ddagger}$ indicates how much bond breaking is occurring in the transition state. The sign of $\Delta S^{\ddagger}$ indicates transition states that are more (negative) or less (positive) ordered than the ground state, and the magnitude offers a measure of the degree to which order is increasing or decreasing. Note: ΔH and ΔS values are typically treated as temperature-independent, whereas ΔG values are at a specific temperature.

Activation parameters are excellent for differentiating between two mechanisms with different degrees of order in the transition state. For example, organic substitutions (S_N1 vs S_N2)[53] and inorganic substitutions (dissociative vs associative)[54] are each readily identified on the basis of the sign of $\Delta S^{\ddagger}$. Note: Entropy values are often considered especially

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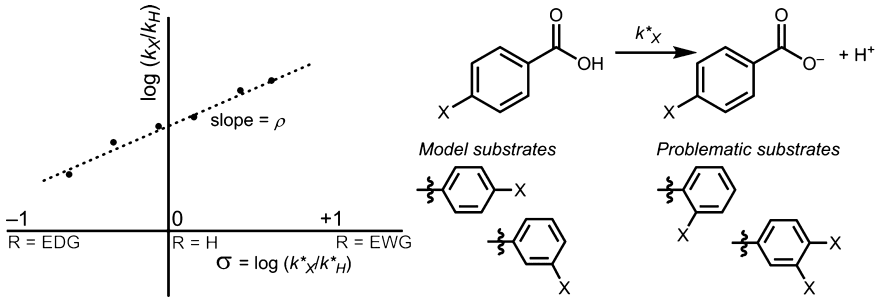

Figure 7. Hypothetical Hammett plot and scheme showing the reference reaction of benzoic acid deprotonation. Model substrates are aromatic groups (especially phenyl) with para- or meta-substitution. Examples of problematic substrates include ortho-substituted arenes, which introduce steric interactions that can disrupt resonance contributions.

prone to error because they are derived by extrapolation to the intercept, yet mathematical treatments may not support this warning.[55] More accurate values are derived from wide temperature ranges and when $|\Delta S^{\ddagger}| > 10$ cal·mol^{-1}·K^{-1}.

A classic example of the use of activation parameters is the Curtin–Hammett principle, which applies to cases where two reactants interconvert rapidly (low barrier relative to others in the reaction coordinate) and each reactant can lead to a distinct product.[56] The ratio of the products depends only on the difference in activation energies ($\Delta\Delta G^{\ddagger}$) between the two product-determining transition states.[57] The Curtin–Hammett principle often explains surprising selectivity or stereochemical outcomes on the basis of an unobserved equilibrium event.[57,58]

Linear Free Energy Relationships (LFERs). Structure–function correlations appear throughout chemistry. LFERs gauge the relative influence of structural changes by comparing the changes in free energy ($\Delta G^{\ddagger}$ or ΔG°) in a series of reactions to a set of reference reactions. *Caution: LFERs compare reactions involving chemically distinct reactants, and structural changes may alter the course of the reaction, invalidating the comparison. Beware of deviations from linearity (curvature), which may indicate a change in mechanism or rds.*

LFER: Electronic Effects and Hammett Plots. Probing the influence of electronic changes requires thermodynamic electronic parameters derived from standard reactions. The Hammett parameter, σ, was developed based on the pK_a of substituted benzoic acids.[59] The original parameter σ, as well as those derived for resonance-stabilized species that develop positive charge (σ^+) or negative charge (σ^-) in the transition state relative to the ground state, is plotted against $\log(k_{obs}/k_H)$ (Figure 7).[60] The slope of the line (ρ) is a measure of how electron-withdrawing groups (EWGs) or electron-donating groups (EDGs) affect the reaction rate. A positive slope indicates that EWGs accelerate the reaction. Larger positive slopes indicate an increased buildup of negative charge in the TS, reflected in higher sensitivity of the rate to EWGs. On the other hand, increasingly large negative slopes indicate a buildup of positive charge in the TS stabilized by EDGs. To avoid conflation with steric effects, only meta- and para-substituted aromatics are considered, with meta-substituted species selectively probing inductive effects.

LFER: Steric Effects. Reactions that are very sensitive to steric bulk often indicate a crowded ground or transition state. A variety of methods for correlating activity with steric bulk are available, including Taft parameters obtained analogously to Hammett parameters.[61] Building on this work, Charton established comprehensive parameters based on van der Waals radii.[62,63] Steric effects in transition metal complexes were first treated by Tolman, who used a "cone angle" term that was estimated based on the size a phosphine ligand fills when bound to a metal ion.[64] Recent work has shown that appropriate steric parameters correlate with enantioselectivity in asymmetric catalysis.[65]

LFER: Acidity or Basicity. Structure–function studies often correlate reactant acidity (pK_a) with reaction rate. The pK_a in water is often quoted, but it is sometimes better to consider the pK_a value in the organic reaction solvent, with nonaqueous pK_a scales available (e.g., DMSO, CH_3CN, THF).[66−68] For reactions involving Lewis acids, relative acidity scales based on the strength of Lewis acid–base adduct formation (e.g., with phosphine oxides) have been developed.[69−71]

Other thermodynamic parameters frequently correlated with reactivity include bond-dissociation free energy (BDFE),[72] hydricity ($\Delta G^{\circ}_{H^-}$),[73,74] and reduction potential (E°).[75] The application of physical organic parameters to asymmetric catalysis has recently been reviewed.[76,77] Another strategy involves structure–function studies in which the rate is measured for a series of reactions with different nucleophiles or leaving groups, as illustrated in the rich mechanistic studies of organic substitution reactions.[78−80] Similar studies probing the effect of incoming or leaving ligands established the mechanism of inorganic substitution.[55,81−83]

When designing an experiment probing a free-energy relationship, consider what parameter(s) might be expected to have a strong correlation with reaction rate; and where structural changes should be probed. Mechanisms may be elegantly differentiated by performing two structure–function studies in tandem: for example, if a substrate of interest contains two aryl rings, separate Hammett plots can be generated for substitution at each aryl ring.[84]

Isotope Effects. Isotope effects comprise differences in reactivity between two isotopes, which stem in large part from differences in mass (and thus vibrational energy levels). Because the mass ratio is largest for ^{1}H and ^{2}H, these isotope effects are most commonly measured.[85] Differences between isotopes are small enough to safely assume that labeled materials will follow the same mechanism as unlabeled materials.

Kinetic isotope effects (KIEs) describe the difference in rate between two isotopically labeled reactants.[86] A KIE is categorized as *normal* or *inverse* based on the magnitude of the ratio k_H/k_D. For $k_H/k_D > 1$, the KIE is considered normal (the deuterated substrate reacts more slowly), and for $k_H/k_D < 1$, the KIE is considered inverse (the deuterated substrate reacts more quickly). Normal isotope effects are most commonly attributed to the heavier isotope having a higher reaction barrier

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(with the heavy isotope being stabilized in the ground state relative to the light isotope). The opposite case is found for inverse isotope effects: the heavier isotope has a lower reaction barrier (with the heavy isotope stabilized in the transition state relative to the light isotope). For example, C−H bond-forming reductive elimination reactions often exhibit an inverse KIE due to a C−H sigma complex that is more stable for the deuterium-containing species.[87,88] Changes in hybridization from sp^2 to sp^3 also commonly give rise to an inverse KIE.[89]

A normal or inverse KIE may be further identified as *primary* or *secondary*. A primary KIE involves cleavage and/or formation of the bond containing the isotopically labeled element. If no bonds to the labeled element are broken or formed, a secondary KIE is observed, based on indirect influences. A normal primary H/D KIE falls between 1.5 and 10, while a normal secondary KIE falls between 1.0 (i.e., no effect) and 1.4. Inverse KIE values follow the same trend, only numerically inverted. Larger KIE values (greater than 100 in some cases) may indicate quantum mechanical tunneling; variable-temperature techniques can distinguish tunneling from other possibilities (such as preceding equilibrium isotope effects or the need to incorporate more complex statistical mechanics models).[90−94]

Three types of KIE experiments can be carried out: (A) two independent experiments to obtain the reaction rate constant for labeled and unlabeled reactants, with the KIE obtained from k_H/k_D (Figure 8A). (B) A competition experiment involving a

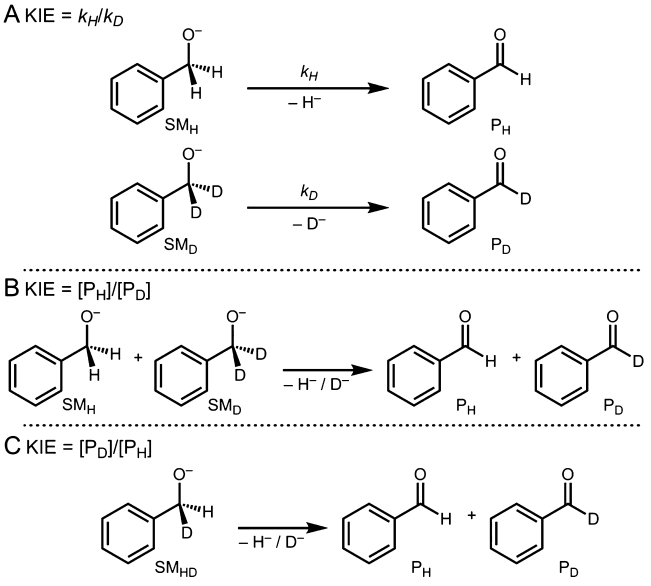

Figure 8. Three different types of KIE experiments.

1:1 mixture of labeled and unlabeled reactants in a single experiment, with the KIE obtained from the ratio of products. The method of initial rates is used to avoid buildup of one reagent or the other, as deviation from a 1:1 ratio would alter the rate independent of any isotope effect (Figure 8B). (C) An internal competition experiment involving a partially deuterated reagent with multiple equivalent reaction sites, where the KIE is also based on the ratio of products (Figure 8C).[86,87]

Each method provides different information.[95] Method A provides information about the rate-determining step: if a KIE is observed, the deuterated position is involved in the rate-determining step. The other two methods do not necessarily provide information about the rate-determining step because isotopic substitution can affect the ratio of products in later steps in some mechanisms.[95−98] Methods B and C are particularly useful in probing the nature of bond-forming or bond-breaking events that are not rate-limiting (and thus cannot be observed by method A).

An equilibrium isotope effect (EIE) may arise from differences in the relative stability of labeled and unlabeled reactants and products. KIE and EIE values are categorized similarly. An EIE is obtained by measuring the equilibrium constant of an unlabeled mixture ($K_{eq,H}$), and comparing $K_{eq,H}$ to that of the labeled system, $K_{eq,D}$: EIE = $K_{eq,H}/K_{eq,D}$. In multistep reactions, such as a pre-equilibrium case, the observed isotope effect will be a composite of KIE and EIE values.[58,93]

Step 5. Design Experiments Capable of Differentiating Remaining Mechanistic Possibilities

In addition to a precise determination of the rate law and an understanding of the nature of the transition state, numerous other techniques are available. Such "supporting methodology" often provides critical evidence for a proposed reaction pathway.

Solvent Effects. Solvent can dramatically impact a reaction. Mechanistic clues are often correlated with the polarity of the solvent: for example, a reaction accelerated by polar solvents suggests charge build-up in the transition state of the rds,[99−102] which can complement Hammett plots.[103]

Labeling Studies. Incorporation of an isotopic label at a judiciously chosen position can give mechanistic insights without kinetic analysis. In most cases, the label is traced to see if bonds to the labeled element are broken, or if isotopic "scrambling" occurs.[104−106] Unlike kinetic isotope effects, which typically require large relative mass ratios, a wide range of isotopes can be employed for labeling studies.

Competition Experiments. Competition experiments are conducted by treating a reactant with a 1:1 mixture of two possible reaction partners.[95,105,107−110] The product distribution is used to determine which of the two possible reactions is faster. Competition experiments are particularly useful when two separate reactions will not suffice, as in cases where the overall reaction is fast or the reaction step of interest occurs after the rds.

Crossover Experiments. For reactions in which two groups couple, crossover experiments employing structurally similar (but chemically distinct) reactants can distinguish between intramolecular and intermolecular pathways. Experimental designs should ensure that the label (whether isotopic or substitutional) does not alter the reaction mechanism, and that the label is sufficient to distinguish the pathways. The most common cases, such as reductive elimination reactions,[88,111−114] require double labeling, i.e., a 1:1 mix of A−A:B−B which forms P_{AA} and P_{BB}; the presence of any P_{AB} would indicate exchange processes or an intermolecular reaction pathway.

Microscopic Reversibility. The "principle of microscopic reversibility" states that a reaction will proceed by the same mechanism in the forward and reverse direction. This principle has been examined by studying reversible reactions, such as (retro)cyclizations and (de)insertions.[115,116] Microscopic reversibility can also be invoked when studying a reaction of interest in the reverse direction.[86,90,117−119]

Probing for Radicals. Radicals are often indicated by irreproducible reaction kinetics, light-sensitive reactivity, or

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induction periods.[120] If including a *radical initiator* eliminates an induction period or leads to smooth kinetics, radicals are likely involved.[121,122] Further tests include the use of a *radical trap*, which can intercept a reactive radical to form a more stable, detectable radical;[123,124] or the use of *radical clocks*,[125] which generate a nonradical product whose structure would be altered by radicals (although the rate constants of the various reactions must be considered when designing these experiments).

Heterogeneity Tests. Many catalysts decompose to metals or metal oxides, which are sometimes responsible for observed reactivity. Finke and others have established an array of rigorous procedures for establishing homogeneity, such as addition of a mercury drop to sequester metallic species or light scattering to look for insoluble particles.[126,127] One often-overlooked test is simple kinetic monitoring, as a "sigmoidal" product growth curve (containing an induction period) is often an indicator of decomposition to an unknown active species.

Computational Techniques. While outside the scope of this guide, theory continues to play an increasingly important role in mechanistic studies.[128−131] Density functional theory calculations are regularly used to probe reaction mechanism; joint experimental−computational approaches are particularly useful.[130,132,133]

Step 6. Re-Assess the Mechanism

Every experiment increases knowledge of a reaction, and assessing progress is often helpful. Can some proposed mechanisms be ruled out? Have the results inspired a new mechanistic hypothesis? The best experiments are *differentiating*. The outcome of an experiment should be consistent with one possible mechanism but inconsistent with another. If the data point to a single mechanism, would other experiments further support (or exclude) this pathway? Is your mechanism consistent with relevant literature examples?

The desired level of mechanistic detail is also a consideration. A reaction analogous to prior examples might only require a few key tests to support the usual mechanism. If the reaction is new or unusual, more detailed kinetics and mechanistic analysis may be in order.

■ USING THE GUIDE AS A PEDAGOGICAL TOOL

The guide to deducing reaction mechanism was written in the process of designing an advanced course entitled "Mechanisms of Organic and Inorganic Reactions" at the University of North Carolina at Chapel Hill. The guide acted as a scaffold for the course outline. Table 2 shows a typical course outline along with the corresponding section from the guide to deducing reaction mechanism.

The first part of the course introduces the tools required to deduce the mechanism of a reaction. The first two weeks provide an opportunity to review electron-pushing schemes, elementary steps, and other background material. This part of the course is more lecture-based. For example, one class might introduce Michaelis−Menten kinetic analysis, with derivations of the steady-state approximation and some examples of graphical analysis. Every fourth class period is used as a problem session: students work in small teams and apply the concepts from lecture to solve problems based on literature examples. The Supporting Information collects some examples of in-class, multipart group problems that utilize a single mechanistic tool, such as kinetic isotope effect studies.

Table 2. Outline of Course Topics from the Authors' Advanced-Level Course[a]

Course Topic	Relevant Section from "Guide to Deducing Mechanism"
Week 1: Electron-pushing in organic reactions	Step 2. Consider various mechanistic possibilities
Week 2: Inorganic structure and mechanism	
Week 3: Simple kinetic systems	Step 3. Kinetic analysis of simple systems
Week 4: Complex kinetic systems	Step 3. Kinetic analysis of complex systems
Week 5: Reaction coordinate diagrams	Step 4. Reaction coordinate diagrams
Week 6: Transition-state theory	Step 4. Transition-state theory and temperature dependence
Week 7: Catalysis	Step 3. Kinetic analysis of catalytic reactions
Week 8: Linear free energy relationships	Step 4. Linear free energy relationships
Week 9: Kinetic isotope effects	Step 4. Kinetic isotope effects
Weeks 10−16: Case studies and proposal project	Step 5. Supporting methodology

[a] Each topic is paired with the corresponding section from the guide to deducing mechanism.

The second part of the course introduces a series of case studies in which the class is encouraged to participate in deciphering a mechanism. Usually, a class period starts with a new reaction, and a simple question: "how does this reaction work?" Students suggest possible pathways and experiments that might differentiate each pathway, and the instructor provides experimental details from the literature to help solve the mystery. For example, in one class period the instructor might draw a proposed mechanism for the Buchwald−Hartwig reaction and ask the class how they would go about testing the hypothesis.[134] Empowered by the knowledge of using Michaelis−Menten kinetics and reaction progress kinetic analysis discussed in the first part of the course, students often suggest these types of experiments. It is not uncommon for students to suggest experiments that were not carried out, which provides an opportunity to speculate on what might have been observed or to discuss why the experiment was not feasible. Lecture materials for this case study are provided in the Supporting Information, along with a bibliography of selected literature examples appropriate for case studies.

The final portion of the course centers on an original proposal for a mechanistic study. Each student picks a paper from the literature that describes a reaction of unknown mechanism. After the paper choice is approved by the instructors, the students write a proposal that includes specific mechanistic studies and explains how each possible outcome would support or refute a particular reaction pathway. Proposals are peer-reviewed and discussed in oral presentations with the class, and the instructors grade both aspects of the work. In this last part of the course, a transition from the inquiry-based case studies to independent learning and self-discovery occurs. Instead of discussing a previously studied catalytic reaction (such as the Buchwald−Hartwig case study), students apply the mechanistic tools they have learned to a new reaction from the literature. This assignment is designed to foster a deeper, more intuitive understanding of how to approach an unknown reaction and to help students discover how to independently apply the tools of mechanistic study without prompting or feedback from instructors. In student

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evaluations, several students have pointed out that the proposal project pushed them to deeply understand the material in the course of applying it independently. Furthermore, the assignment also is designed to strengthen critical reading and scientific writing skills.

Structuring the course around a practical guide to mechanistic study and real world examples has been instrumental in achieving a lively classroom environment. Key concepts are solidified through repeated discussion and through students applying the methods themselves. Exam questions are designed to test students on their creative thinking and problem solving, in addition to their fundamental understanding of mechanistic probes. As can be seen in the example questions included in the Supporting Information, the questions typically require the use of multiple tools of mechanistic analysis and often ask the student to suggest a mechanism or an experiment.

A qualitative assessment of student enthusiasm and engagement can be obtained from university course evaluation data. In 2012, the instructors taught the same course together, covering essentially the same material with a different course outline and with fewer case studies and no proposal project. The course evaluation data from the 2013 and 2014 courses, which implemented the pedagogical changes descried above, revealed that students felt more engaged in the course, found the material more exciting, connected more deeply to the examples, and gave the course a higher overall rating. Several students commented on the value of the case studies and the proposal project in providing a deeper understanding of the material. We believe that the ability to consider complex mechanistic questions systematically, paired with proposal writing skills gained in the course, can help prepare students for future studies and independent research endeavors, although rigorous educational research studies would have to be conducted to address this directly.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.5b00160.

"Rules of thumb" that help build chemical intuition, bibliography of detailed mechanistic studies, group problem solving questions and exam questions, fitting data discussion, and derivations of approximations for reactions (PDF)

Lecture materials (PDF)

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Notes

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