Visual Methods for the Analysis of Reaction Kinetics

Reaction Progress Kinetic Analysis (RPKA) and Variable Time Normalization Analysis (VTNA)

Literature Review

Justin Wang

6/21/24

Key Literature and Tutorials

Reaction Progress Kinetic Analysis

- *ACIE* **2005**, *44*, 4302.
- *JACS* **2015**, *137*, 10852.
- Wikipedia

Variable Time Normalization Analysis

- *ACIE* **2016**, *55*, 16084.
- *Chem. Sci.* **2019**, *10*, 4348.
- *ACIE* **2019**, *58*, 1018.

How to Apply Either Method

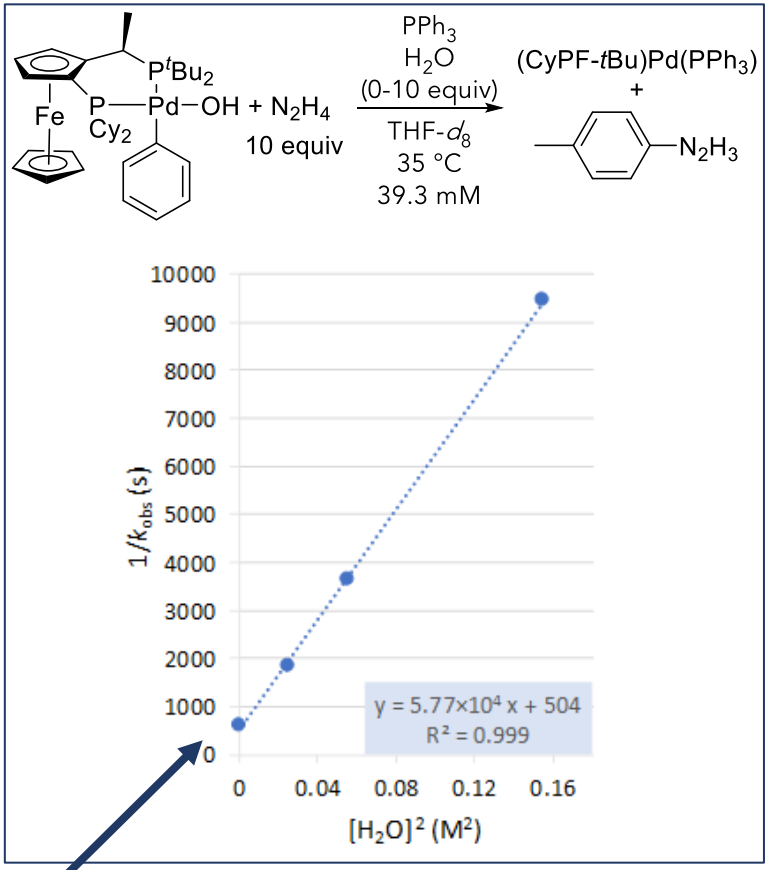
From the SI of *Chem. Sci.* **2019**, *10*, 4348.

- Video Tutorial https://youtu.be/5ORFRB4U10s
- Excel file

Why Use Visual Methods for Kinetics?

Rate measurements at varying concentrations of a reagents

- Tedious and time consuming



Each data point measures the conversion of SM to product over ~4 half lives = ca. **8-10 h** for the entire data set

Why Use Visual Methods for Kinetics?

Rate measurements at varying concentrations of a reagents

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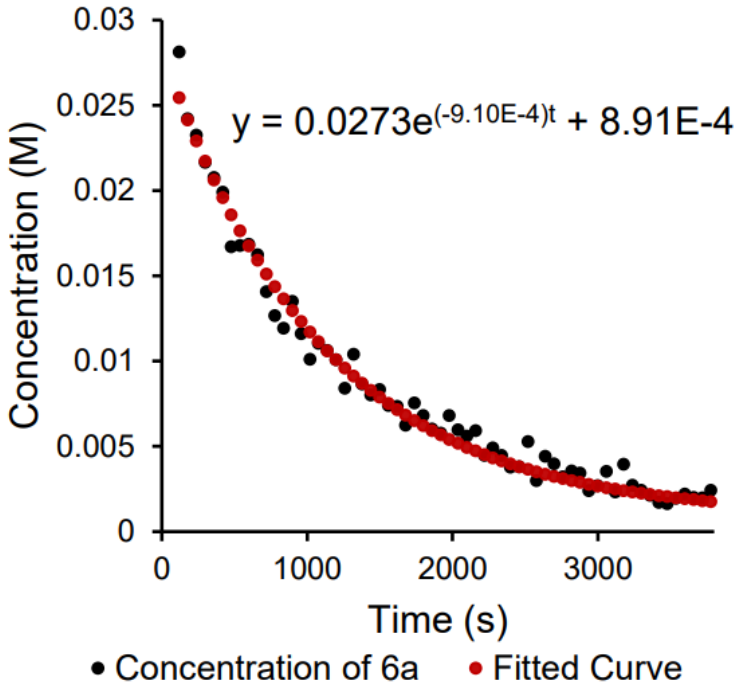
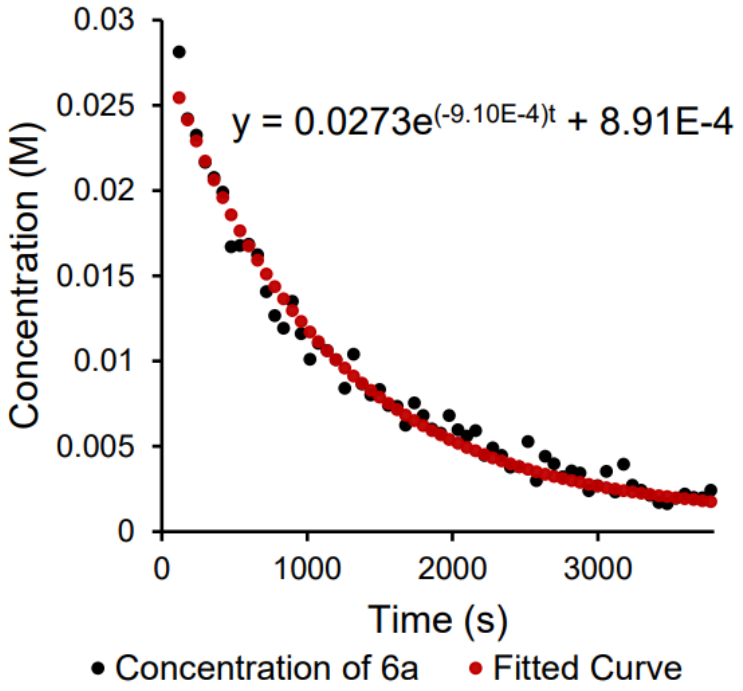
- Often require well-behaved reactions (high mass balance, no side reactions)



Why Use Visual Methods for Kinetics?

Rate measurements at varying concentrations of a reagents

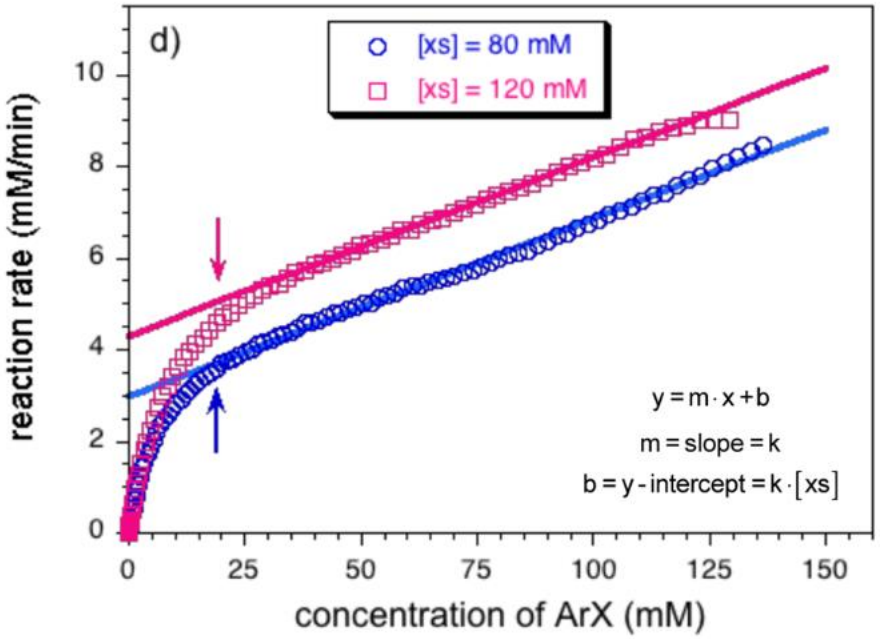
- Tedious and time consuming
- Often require well-behaved reactions (high mass balance, no side reactions)
- Bimolecular reactions are often modelled with initial rate kinetics or by the method of flooding (pseudo-first order kinetics)



Why Use Visual Methods for Kinetics?

Graphical Methods

- Requires substantially less data (minimum of 2 data sets)
- Can be used for complicated kinetics (cat. deactivation, product inhibition, etc.)
- Measures kinetics of reactions at synthetically relevant conditions



Two data sets can be used to extract reaction order.
Time investment = **70 min**

What are Orders in Reagents?

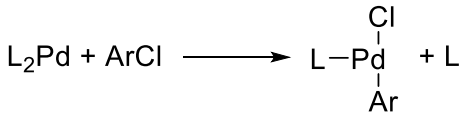
The order in a reagent describes how the rate of a reaction changes based on the concentration of that reagent

$$Rate = \frac{d[Product]}{dt} = [A]^{\alpha}[B]^{\beta}$$

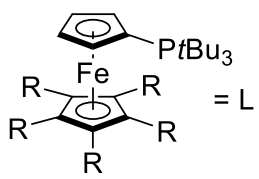
- In this example, the order in [A] is α and the order in [B] is β.
- Not to be confused with the ***reaction*** order, which is α + β

Stoichiometric Reaction

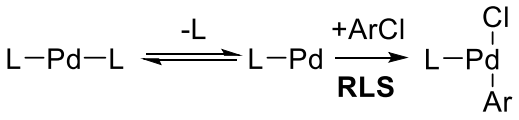
- Order in a reagent *often* represents the stoichiometric relationship between reactant(s) and the structure of the transition state of the rate-limiting step.

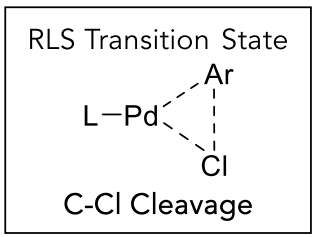


Order in [L] = -1
Order in [ArCl] = 1



R = *p*-tolyl





JACS **2005**, *127*, 6944.

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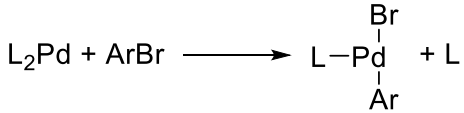
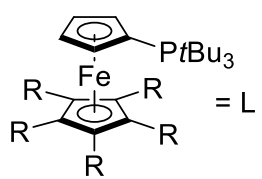


Order in [L] = 0
Order in [ArBr] = 0



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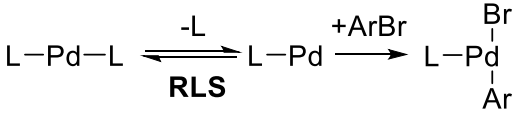

RLS Transition State

L—Pd- - -L

Ligand Dissociation

JACS **2005**, *127*, 6944.

What are Orders in Reagents?

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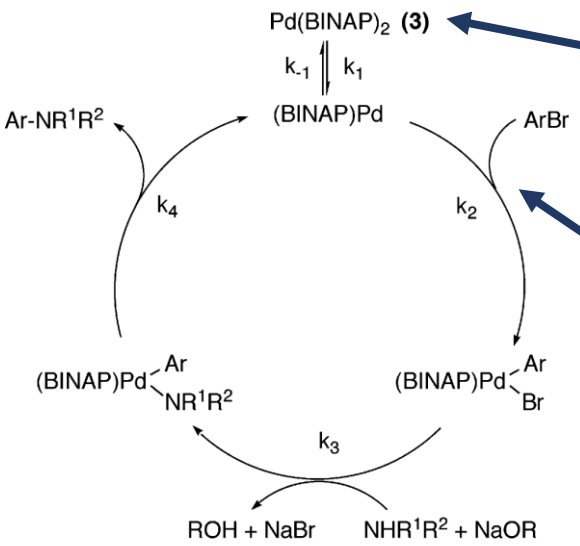
Catalytic Reaction

- Stoichiometric relationship between the **catalyst resting state** and the structure of the transition state of the rate-limiting step



Cat. Resting State

Rate Limiting Step

Reaction is 1st order in [ArBr], inverse 1st order in [BINAP], and 0th order in [Amine]

JACS **2006**, *128*, 3584.

What are Orders in Reagents?

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Catalytic Reaction

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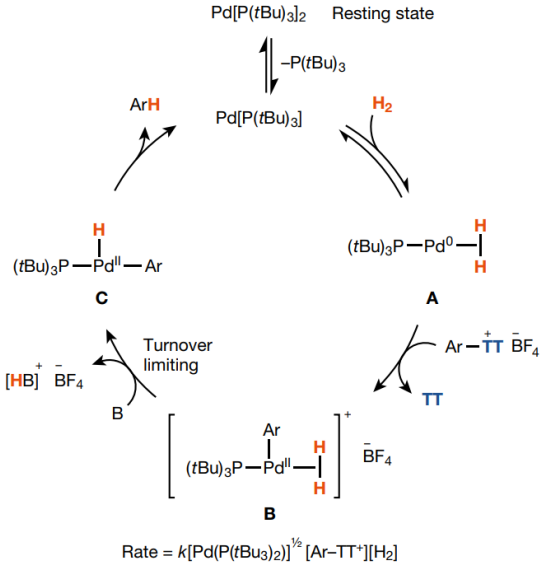


Order in [L_2Pd] = 0.5 even though dimer dissociation is not present

$L_2Pd \rightleftharpoons LPd + L$ (K_{eq})

L = P*t*Bu$_3$

Reaction is 1st order in [LPd].
[LPd] = $K_{eq}[L_2Pd]/[L]$ and [LPd] = [L] at all times, thus $[LPd]^2 = K_{eq}[L_2Pd]$.
Therefore $[LPd] = (K_{eq}[L_2Pd])^{0.5}$

For further discussion see the SI and peer review file:
Nature **2021**, *600*, 444.

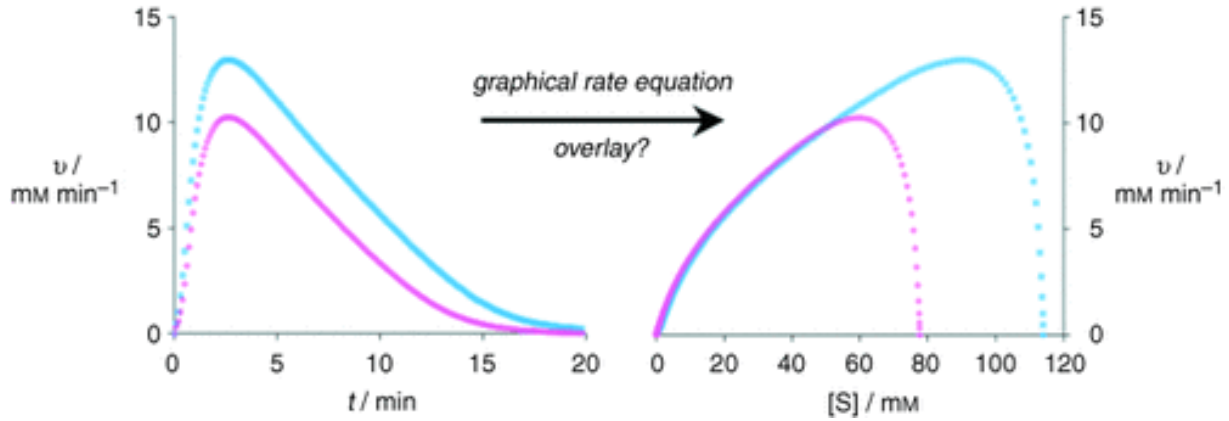
Reaction Progress Kinetic Analysis

Donna Blackmond
Scripps Research - La Jolla

"Reaction progress kinetic analysis is faster, requires fewer experiments, can provide enhanced mechanistic detail, and is arguably more accurate than classical kinetic techniques. Why, then, have these methods not yet become common practice in studies of organic reactions? ***The answer to this question lies, I believe, in our general difficulty in relating the mathematics of a reaction rate law to the molecular story unfolding within a catalytic reaction system***. Kinetics conjures up images of experimental drudgery, mathematical manipulations, and logarithmic graphs; chemists prefer to spend their time devising novel transformations in the laboratory. "

ACIE **2005**, *44*, 4302.

Reaction Progress Kinetic Analysis

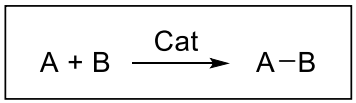


- Graphical manipulation of time course data involving rate vs. concentration of a substrate

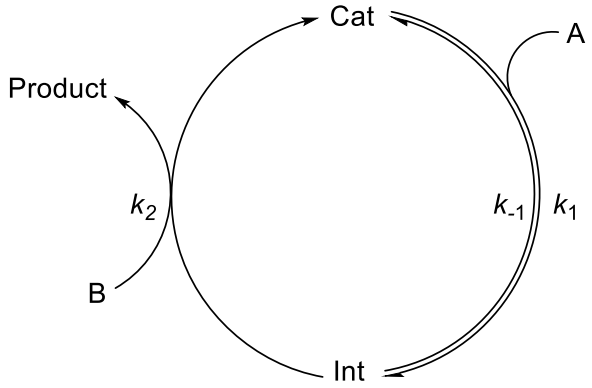
- Visual method for determining the order in a reagent or to identify catalyst deactivation or product inhibition by overlaying kinetic profiles from two reactions.

JACS **2015**, *137*, 10852.
ACIE **2005**, *44*, 4302.

Math Basis for RPKA



$$\text{rate} = \frac{k_1 k_2 [A][B][Cat]_{tot}}{k_{-1} + k_1[A] + k_2[B]} \qquad [Cat]_{tot} = [Cat] + [Int]$$



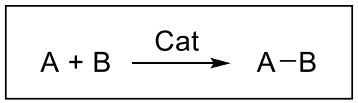
- Uses a parameter called "excess" to reduce number of variables
- In this case [A] and [B] vary over the course of the reaction, but the variation is not independent of each other

$[Excess] = [B]_{t=0} - [A]_{t=0} = [B]_t - [A]_t$

[Excess] can be negative, positive, or zero, but *remains constant* across the course of the reaction.

Therefore, [B] = [Excess] + [A] at all times.

Math Basis for RPKA

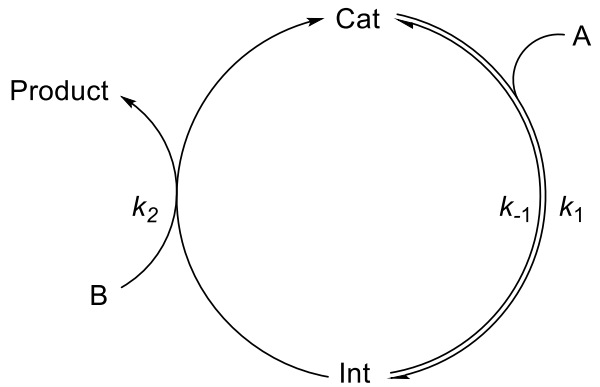


$$\text{rate} = \frac{k_1 k_2 [A][B][Cat]_{tot}}{k_{-1} + k_1[A] + k_2[B]}$$

$[Cat]_{tot} = [Cat] + [Int]$

Substitute in
$[B] = [Excess] + [A]$

$$\text{rate} = \left(\frac{[Excess][A] + [A]^2}{1 + b[A]} \right) a[Cat]_{tot}$$

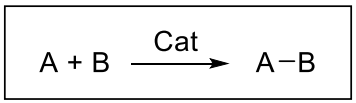


$$a = \frac{k_1 k_2}{k_{-1} + k_2[Excess]}$$

$$b = \frac{k_1 + k_2}{k_{-1} + k_2[Excess]}$$

- Rate law can now be written as a function of one reagent, [A].
- Still, there are multiple independent variables (k_1, k_{-1}, *and* k_2) that are unknown
- **Reactions at different values of [Excess] can be used to determine order in [A] or [B]**

Math Basis for RPKA



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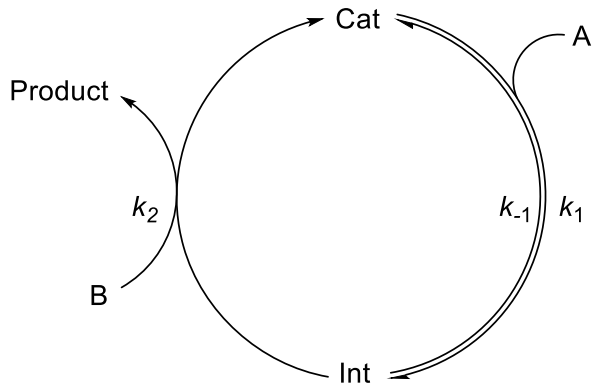


$$a = \frac{k_1 k_2}{k_{-1} + k_2[Excess]}$$

$$b = \frac{k_1 + k_2}{k_{-1} + k_2[Excess]}$$

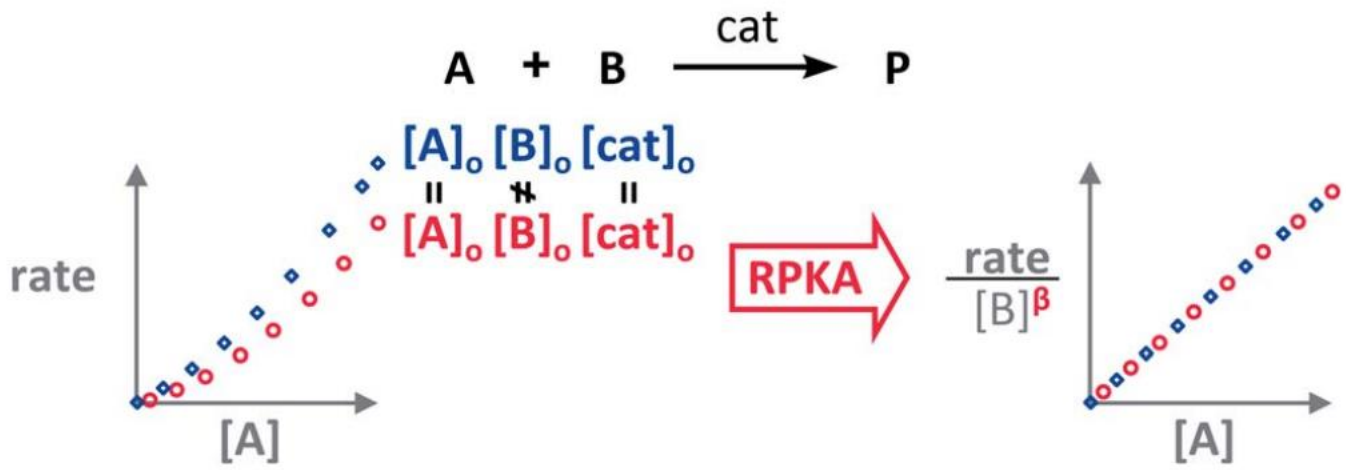
IMPORTANT:
In reactions where A and B do not react in a 1:1 manner,

$[Excess] = [B] - (n_A/n_B)[A]$

where n_A and n_B are the stoichiometric coefficients for A and B, respectively

Chem. Sci. **2019**, *10*, 4348.

Using RPKA to Determine Order in a Reagent – Different Excess Experiment



To Find Order in [B]

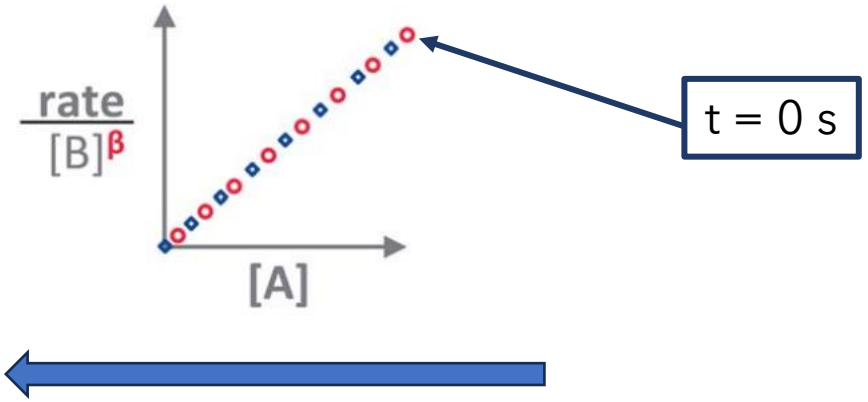
1. Conduct two or more experiments at different [Excess], *where the only change in concentration is in [B].* Obtain rate vs. [A] data.

2. Plot rate/$[B]^{\beta}$ vs. [A]

3. Manually adjust the value of β until the plots overlay. When the plots overlay, β = the order in [B]. *Good overlay is subjective.*

4. Repeat the same procedure to plot rate/$[A]^{\alpha}$ vs. [B] to obtain α, the order in [A] or plot rate/$[cat]^{\gamma}$ vs. [B] or [A] to obtain γ, the order in [cat]

Using RPKA to Determine Order in a Reagent – Different Excess Experiment



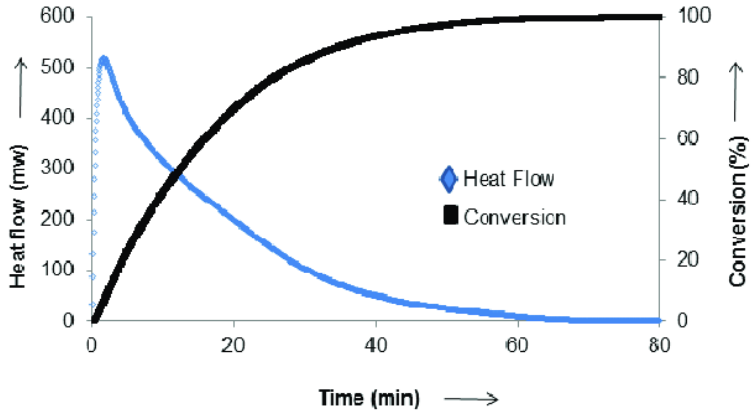
Increasing Time

Plots are read right to left

- As consumption of a reagent increases, rates typically decrease.

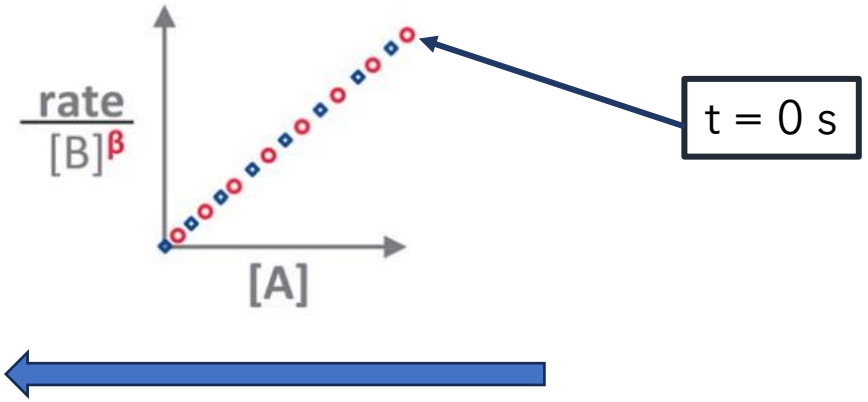
Rate data is needed

- Typically, calorimetry is used, where heat flow is directly proportional to rate. Conversion is found by integrating a plot of heat flow vs. time.



Heat Flow → $\dot{q} = \Delta H_{rxn} \cdot V \cdot r$ ← Rxn Rate

Using RPKA to Determine Order in a Reagent – Different Excess Experiment



Increasing Time

Plots are read right to left

- As consumption of a reagent increases, rates typically decrease.

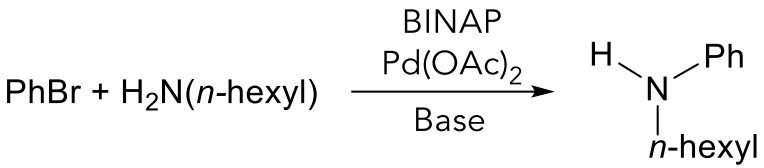
- Spectroscopic methods that measure concentration must be processed to the first derivative to find rate and this must be correlated to concentration

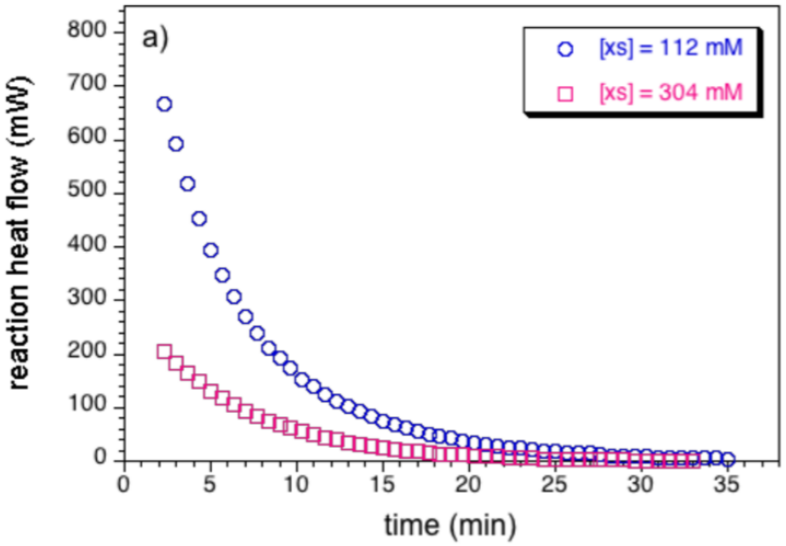
$$Rate = \frac{d[P]}{dt}$$

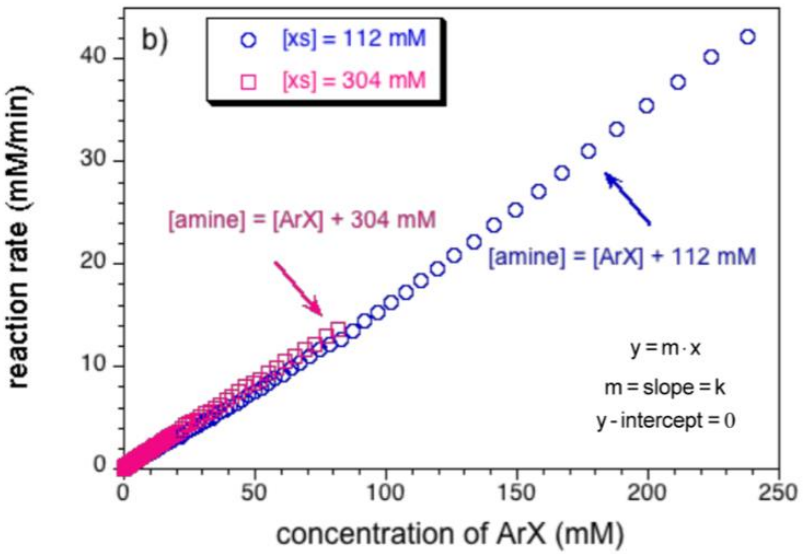
- Alternatively, one can find the tangent

$Rate = \frac{[P]_{t=n+1} - [P]_{t=n}}{t_{n+1} - t_n}$, where P is product

Example of Reagent Order Determination – C-N Coupling Reaction







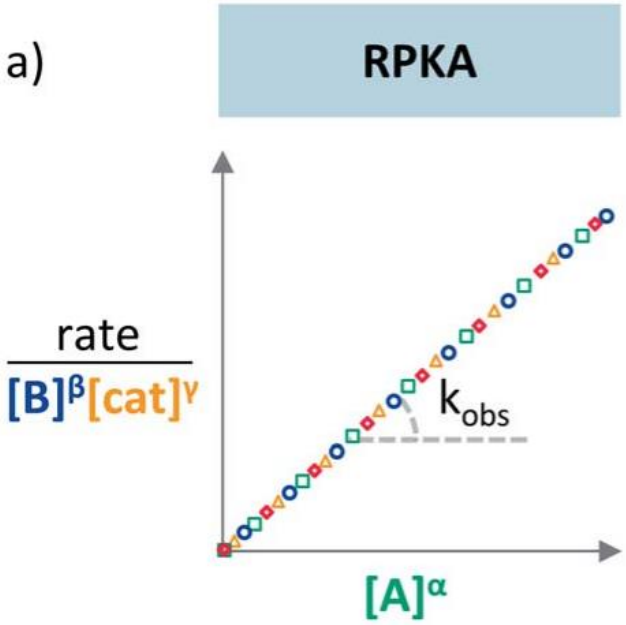
Plot of rate vs. [ArX] overlays *and is linear*.

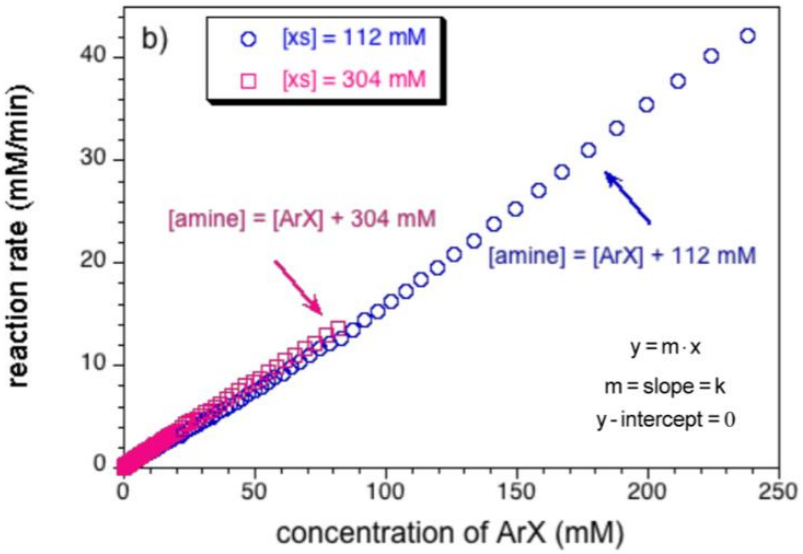
1. This indicates the reaction is 0 order in [amine].

2. The reaction is also 1st order in [ArX].
   This is because the lines are linear.

JACS **2015**, *137*, 10852

Example of Reagent Order Determination – C-N Coupling Reaction





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Linear plots are obtained when *all concentration variables are raised to the correct power*

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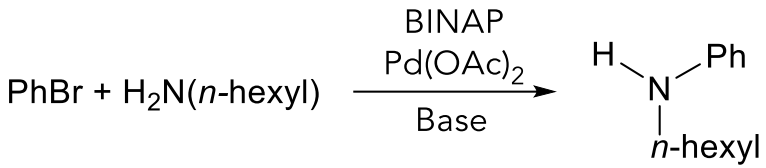

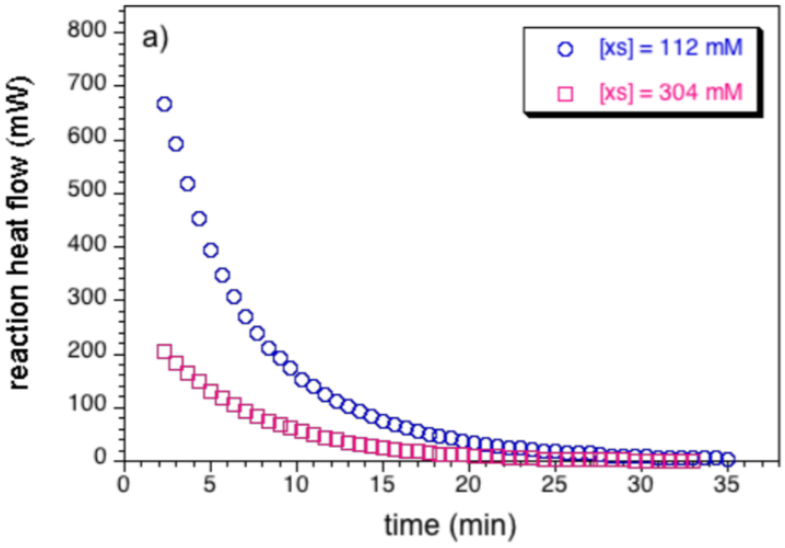

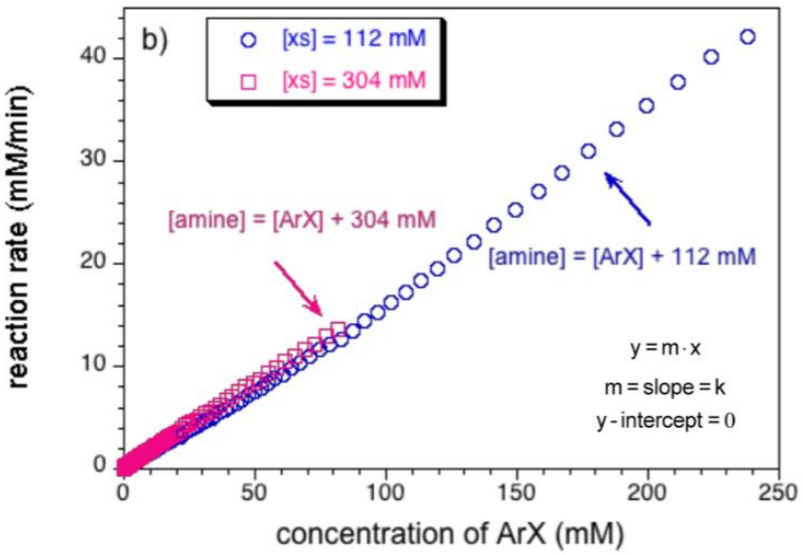

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1. This indicates the reaction is 0 order in [amine].

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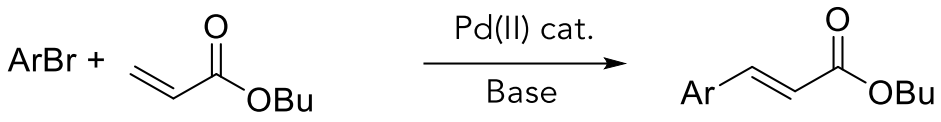
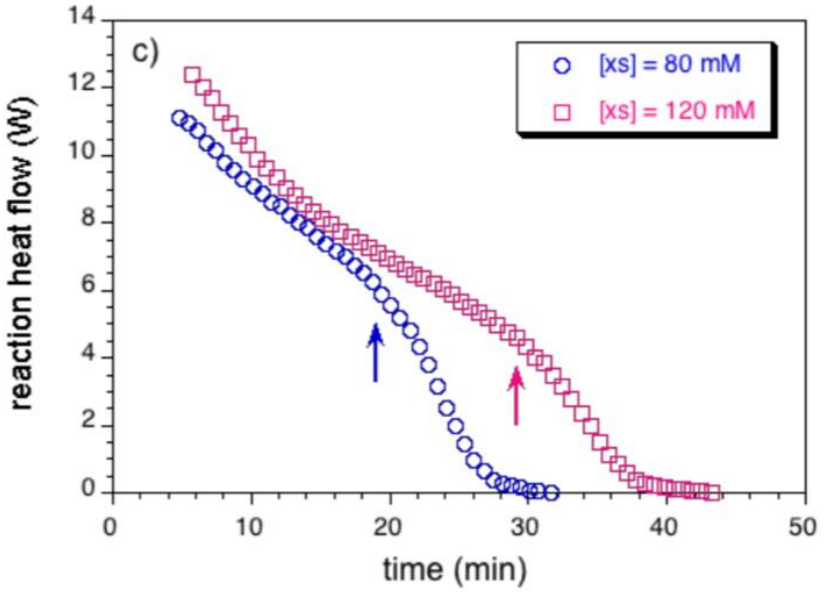
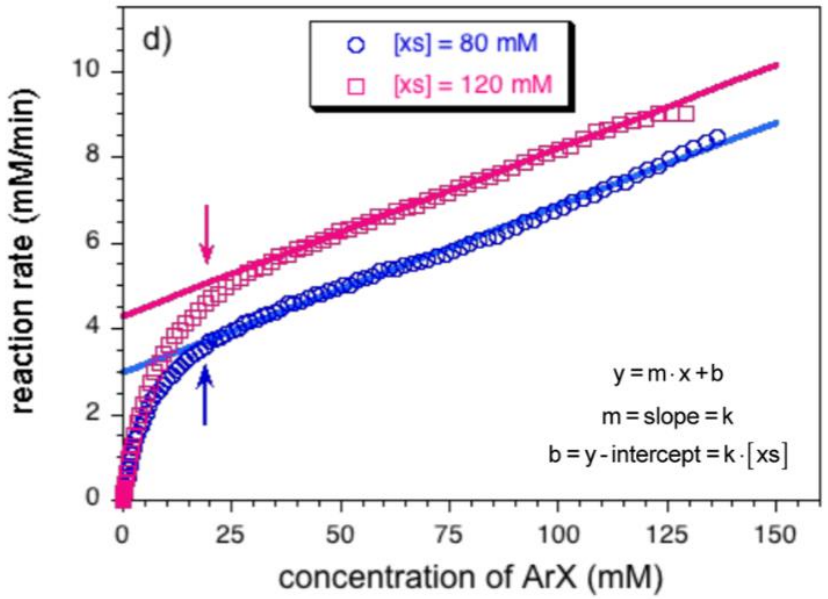
3. These orders are constant throughout the ***overlaid*** section of reaction

Example of Reagent Order Determination – Heck Reaction







Plot of rate vs. [ArX] does not overlay until later portions of the reaction.

1. This indicates the reaction is 0 order in [olefin] and 1st order in [ArX] at later stages of reaction

JACS **2001**, *123*, *1848*.

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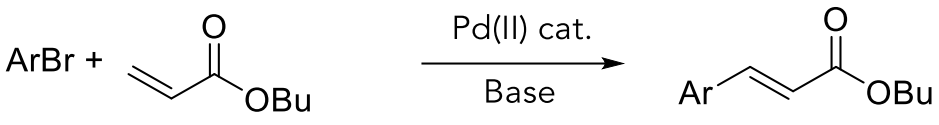
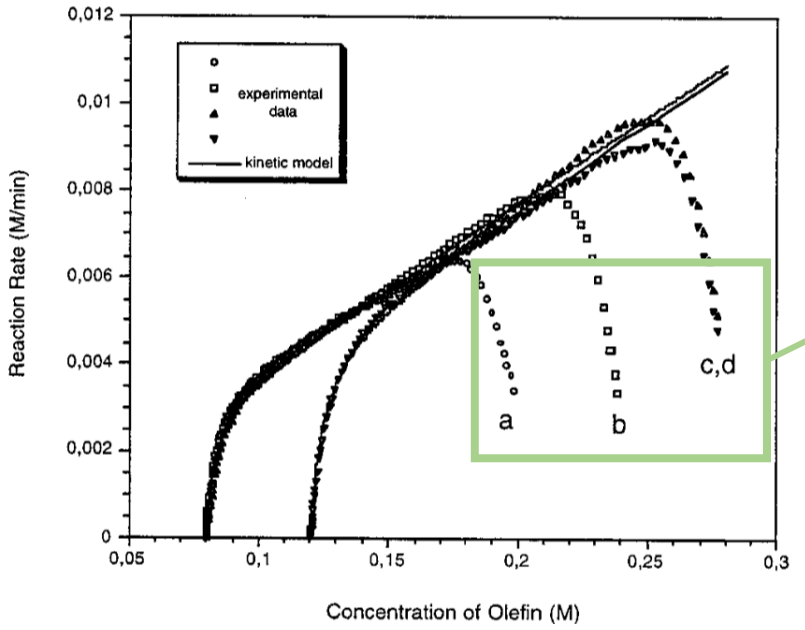




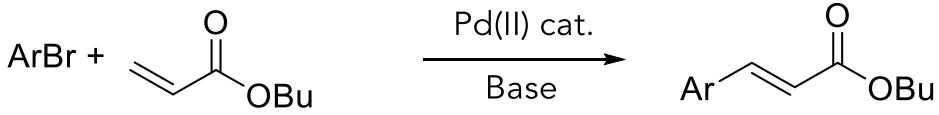
Reaction induction period. Not used in analysis.

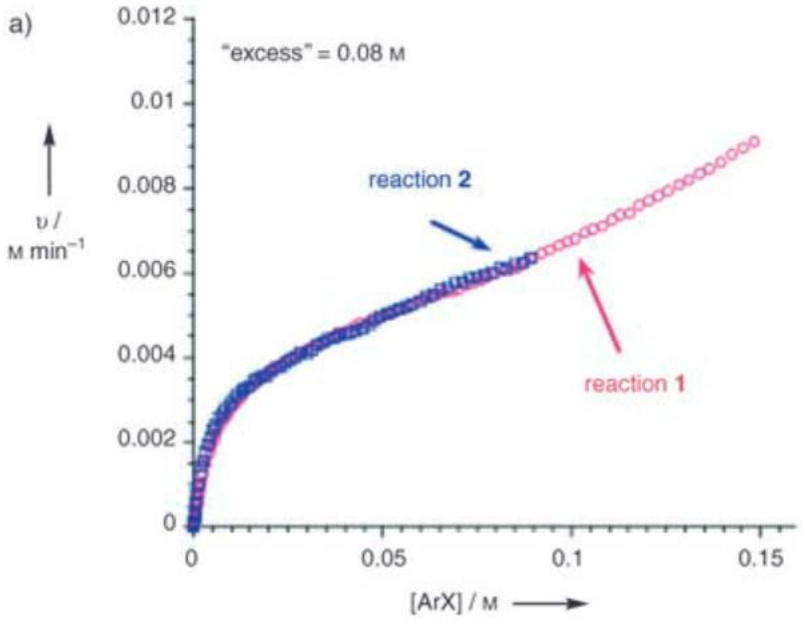
JACS **2001**, *123*, *1848*.

Plot of rate vs. [ArX] does not overlay until later portions of the reaction.

1. This indicates the reaction is 0 order in [olefin] and 1st order in [ArX] at later stages of reaction
2. The linear portions overlay in this rate vs. [olefin] plot. This means at earlier stages the reaction is 0 order in [ArX] and also 1st order in [olefin]
3. The order in [ArX] varies over the course of the reaction from 0 to 1. This is saturation kinetics.

Probing for Catalyst Deactivation or Product Inhibition – Same Excess Experiment





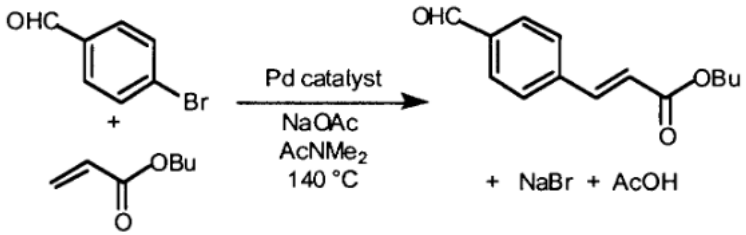
- Catalyst deactivation or product inhibition can be probed by comparing two reactions. One of which is the other reaction at partial conversion **but with [excess] held at the same value**.
- [Catalyst] is held at constant value across the two experiments.
- Overlay = uninhibited catalysis

Entry	$[ArX]_0$ (M)	$[Olefin]_0$ (M)	[Excess] (M)
1	0.15	0.23	0.08
2	0.08	0.16	0.08

Entry 2 is just entry 1 after 0.07 M of [ArX] and [Olefin] have been consumed

JACS **2015**, *137*, 10852

Probing for Catalyst Deactivation or Product Inhibition – Same Excess Experiment



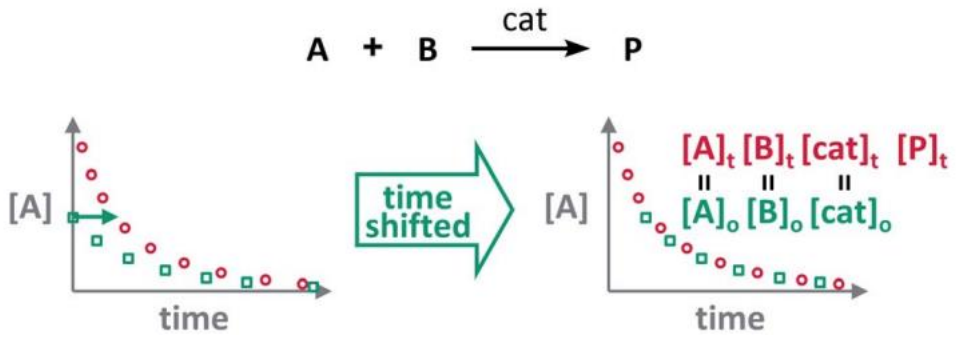
If there is no overlay:

- Repeat the "partial conversion" experiment with product present (entry 3).
  - If entry 3 overlays with entry 1, then product inhibition is present.
    - No overlay = catalyst deactivation

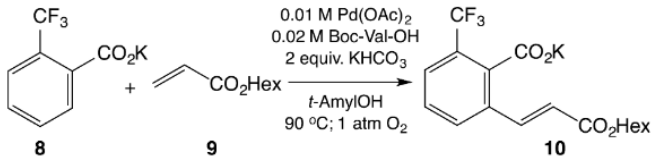
Entry	$[ArX]_0$ (M)	$[Olefin]_0$ (M)	$[Product]_0$ (M)	[Excess] (M)
1	0.15	0.23	0	0.08
2	0.08	0.16	0	0.08
3	0.08	0.16	0.07	0.08

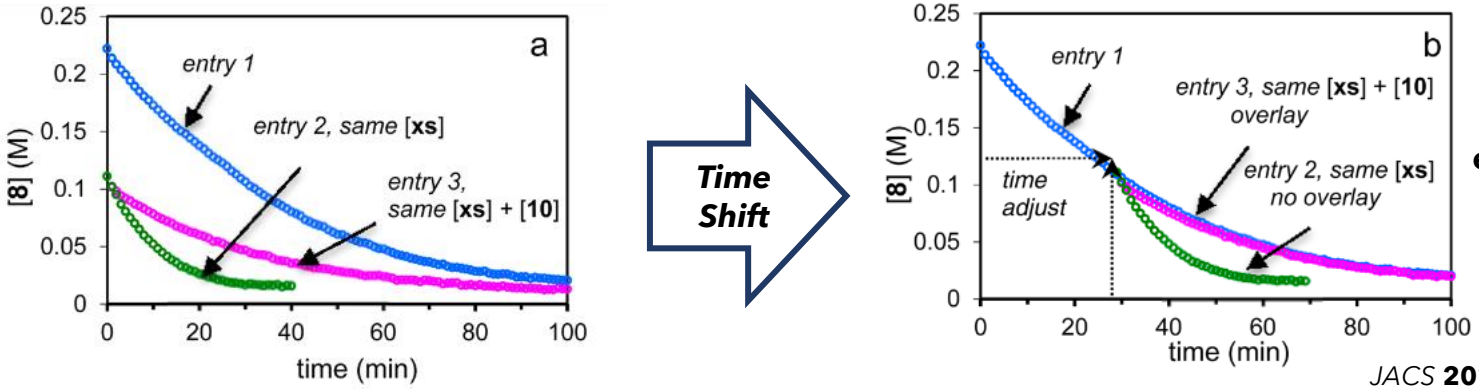
JACS **2015**, *137*, 10852

Probing for Catalyst Deactivation or Product Inhibition – Same Excess Experiment



- Same procedure can be done with concentration vs. time curves to probe for cat. deactivation or product inhibition.
- However, the curve for the "partial conversion" reaction must be time shifted

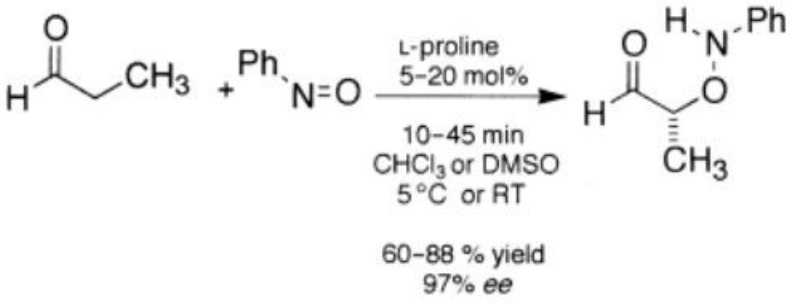


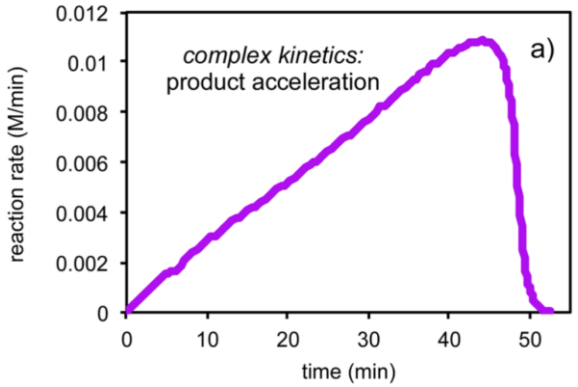


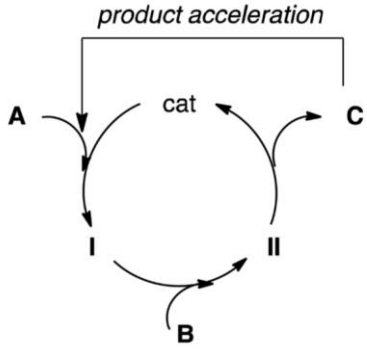
This is an example of product inhibition

JACS **2015**, *137*, 10852

RPKA – Complex Cases







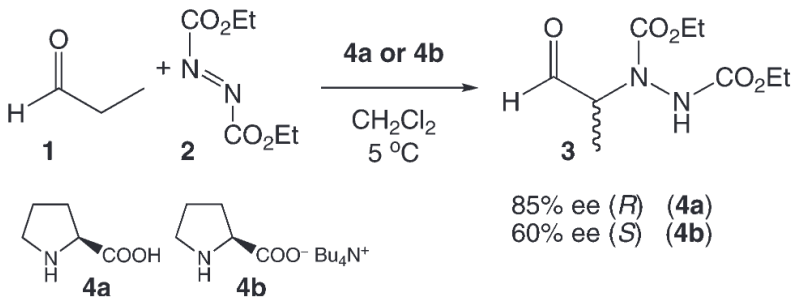
Product Acceleration

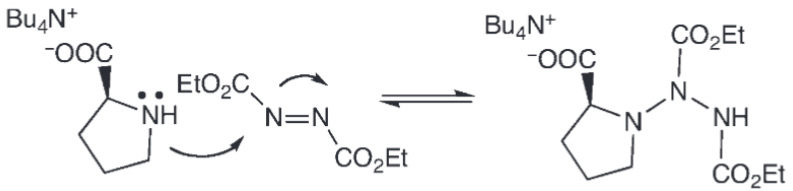
(arguably autocatalytic)

Product of the reaction + proline catalyzes the reaction better than proline + substrate

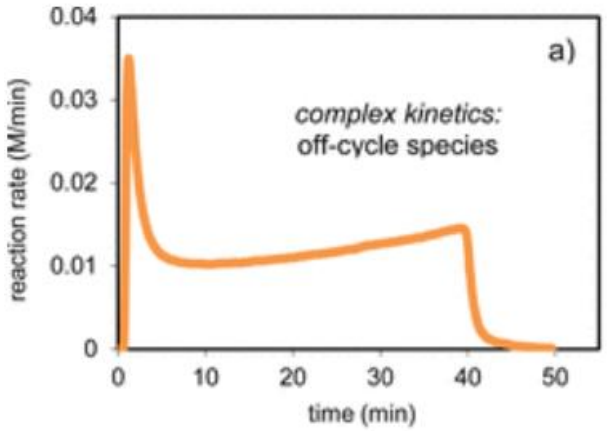
ACIE. **2004**, *43*, 3317.

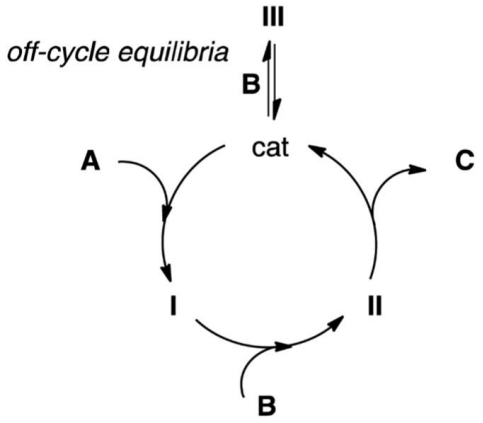
RPKA – Complex Cases





Equilibrium between on and off-cycle catalyst



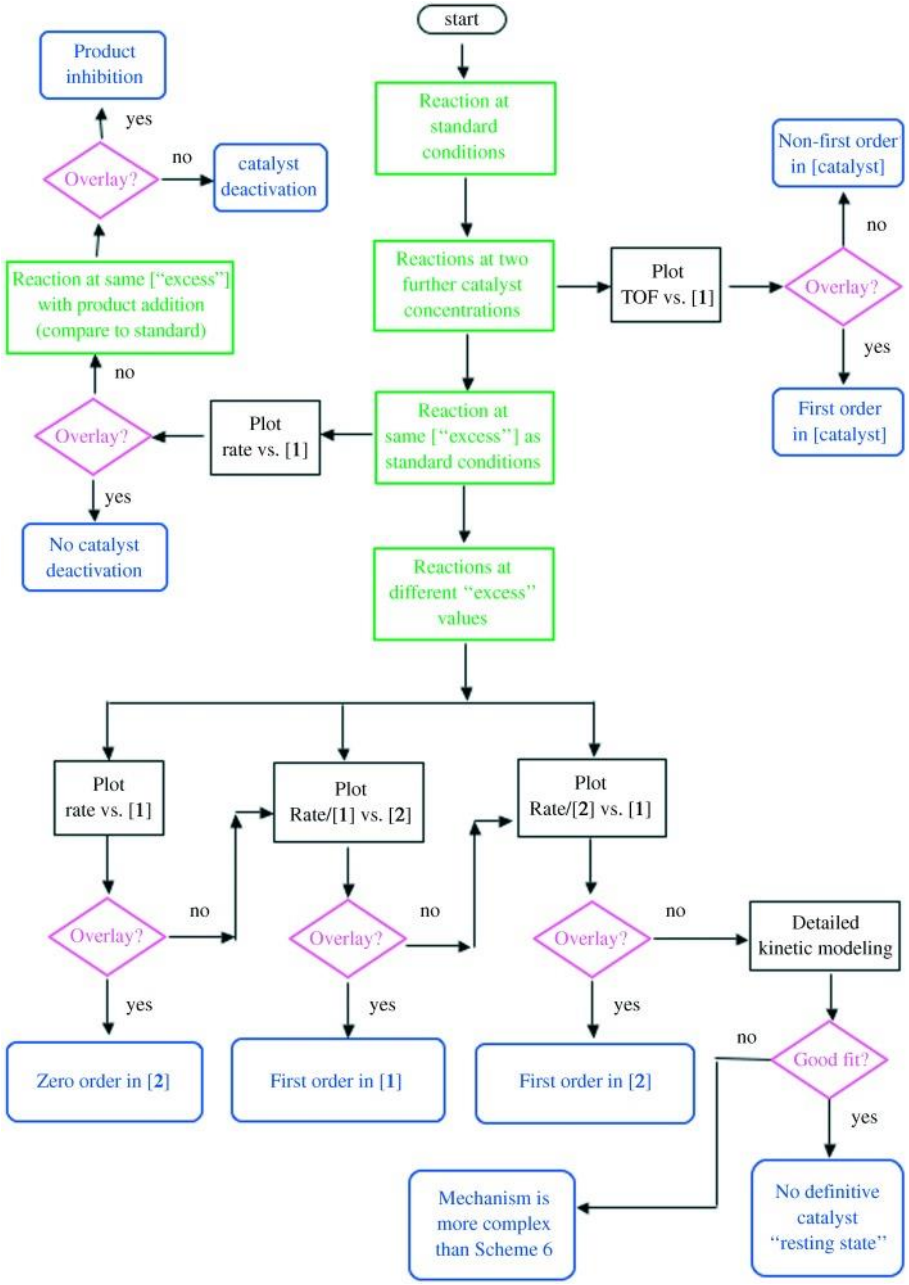


Temporary Rate Enhancement

Non-intuitive rate vs. time behavior can be explained due to catalyst shuttling between on and off-cycle species.

Org Lett. **2011**, *13*, 4300.

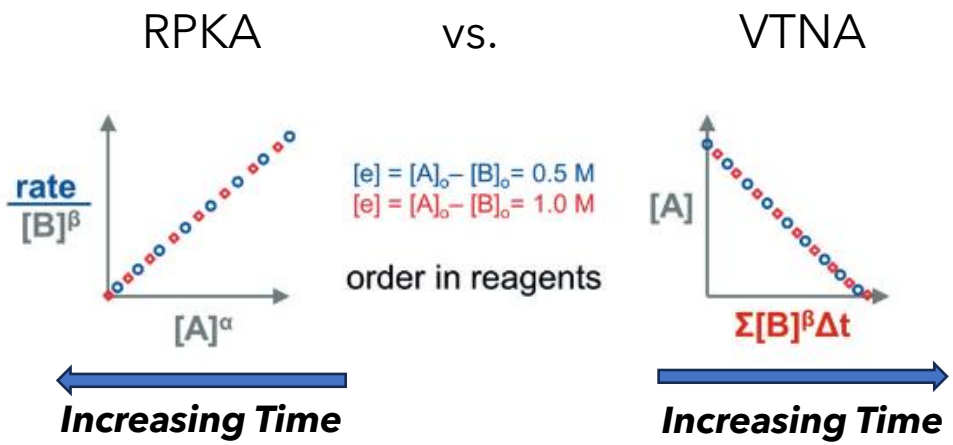
Order of Operations for RPKA



ACIE **2005**, *44*, 4302.

Variable Time Normalization Analysis (VTNA)

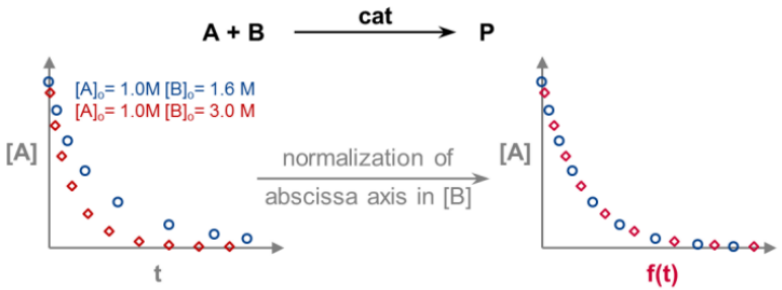
Jordi Burés
University of Manchester



- Utilizes concentration vs. "time" plots instead of rate vs. concentration
- Easier to obtain from workhorse spectroscopic techniques like NMR spectroscopy
- "RPKA" but more accessible instrumentation and literature-wise

ACIE **2016**, *55*, 16084.

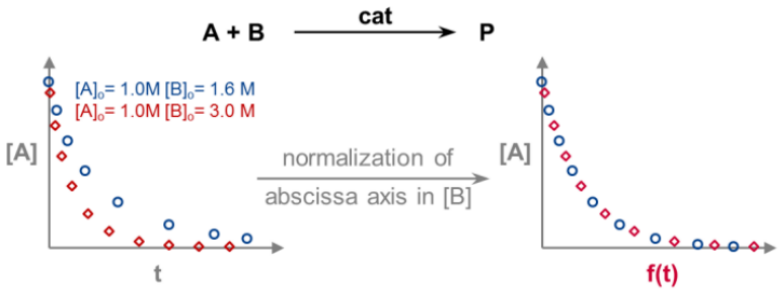
Variable Time Normalization Analysis (VTNA) – Math Basis



- Time normalization "removes" the effect of one reagent on *rate when raised to the correct power*
- This is the origin of graphical overlay

ACIE **2016**, *55*, 16084.

Variable Time Normalization Analysis (VTNA) – Math Basis



$$-\frac{dA}{dt} = k[A]^{\alpha}[B]^{\beta} \quad (1)$$

$$-\frac{dA}{df(t)} = k[A]^{\alpha} \quad (2)$$

$$df(t) = [B]^{\beta}dt \quad (3)$$

$$f(t_n) = \int_0^{t_n} [B]^{\beta}dt \approx \sum_{i=1}^{n} \left(\frac{[B]_i + [B]_{i-1}}{2}\right)^{\beta} (t_i - t_{i-1}) \quad (4)$$

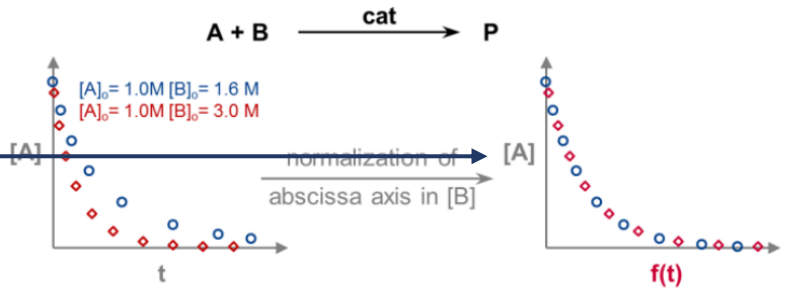
Figure S1. Mathematical demonstration of the change of variable performed in order to remove the effect in **[B]**.

- Time normalization "removes" the effect of one reagent on *rate when raised to the correct power*
- This is the origin of graphical overlay

ACIE **2016**, *55*, 16084.

Variable Time Normalization Analysis (VTNA) – Math Basis

Vertical axis can be [A], [B], or [P], whichever is easiest to obtain



$$-\frac{dA}{dt} = k[A]^{\alpha}[B]^{\beta} \quad (1)$$

$$-\frac{dA}{df(t)} = k[A]^{\alpha} \quad (2)$$

$$df(t) = [B]^{\beta}dt \quad (3)$$

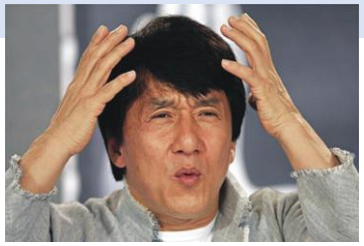
$$f(t_n) = \int_0^{t_n} [B]^{\beta}dt \approx \sum_{i=1}^{n} \left(\frac{[B]_i + [B]_{i-1}}{2}\right)^{\beta} (t_i - t_{i-1}) \quad (4)$$

Figure S1. Mathematical demonstration of the change of variable performed in order to remove the effect in **[B]**.

Summation of average of [B] at time = *i* and the data point prior to *i* raised to the power of β

Time interval between data points

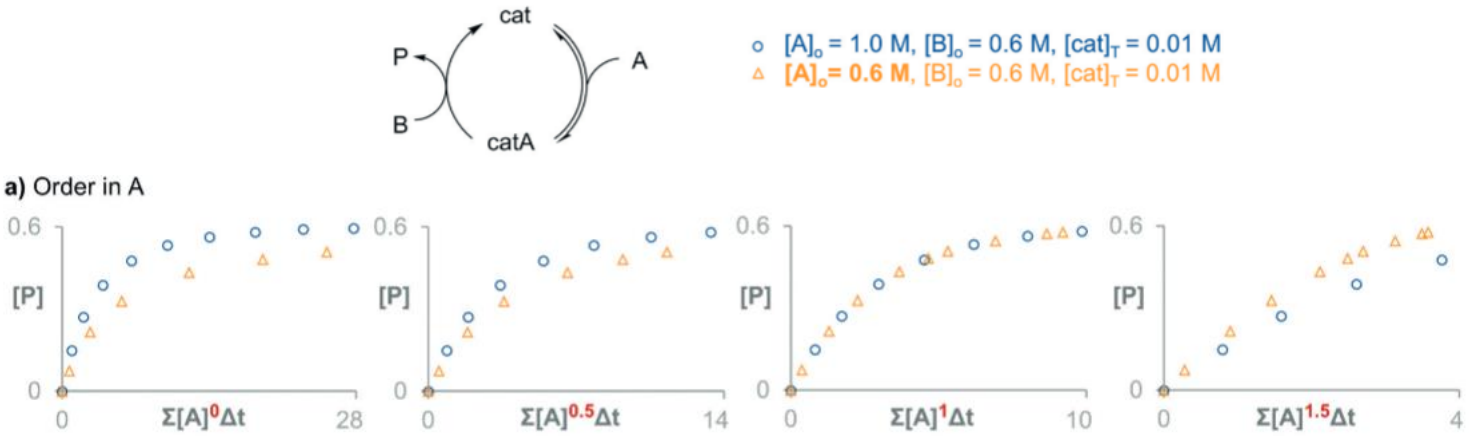
- Time normalization "removes" the effect of one reagent on rate *when raised to the correct power*
- This is the origin of graphical overlay



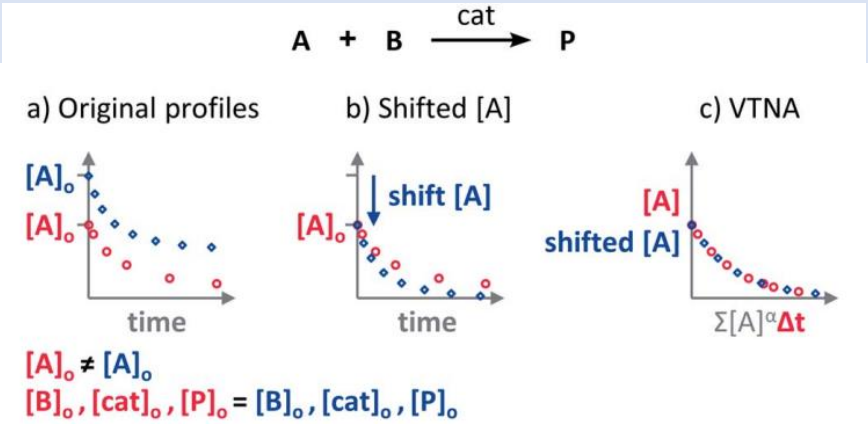
Video tutorial on doing this in Excel
https://youtu.be/5ORFRB4U10s

Chem. Sci. **2019**, *10*, 4348.
ACIE **2016**, *55*, 16084.

VTNA in Action

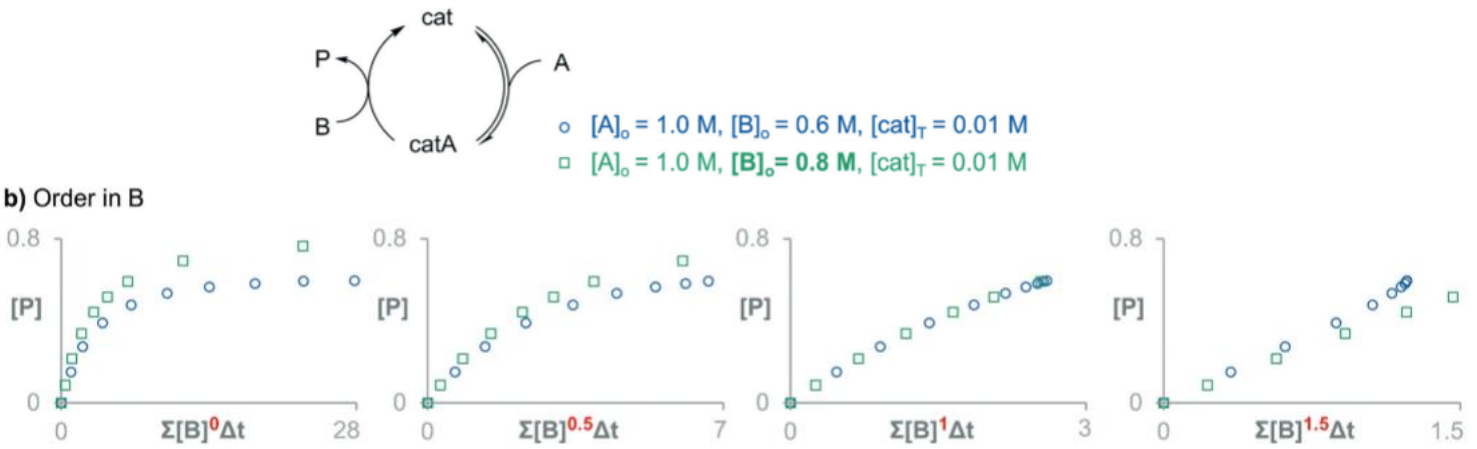


- Comparison of two reactions with differences in [A] only
  - **The order in [A] is one** as this leads to an overlay
  - **VTNA can only be applied to curves with the same starting point**

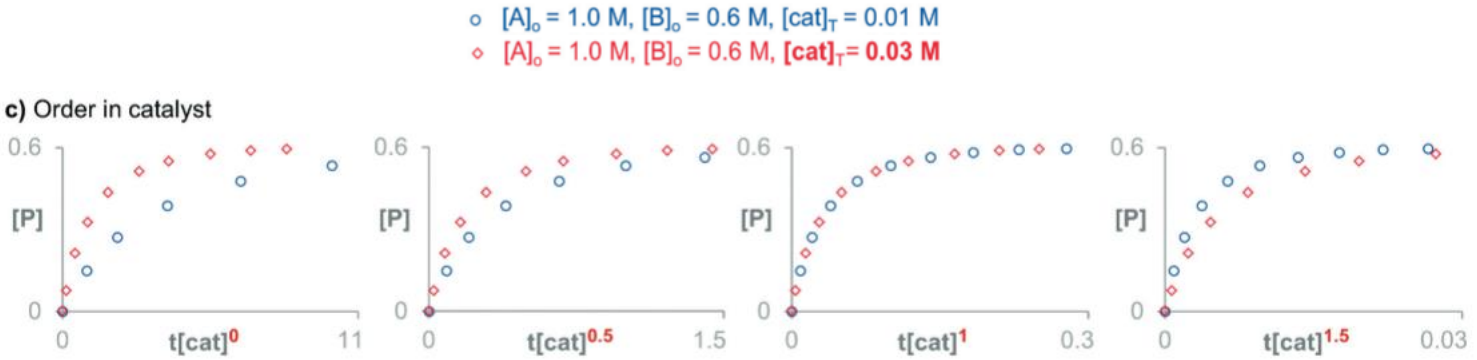


ACIE **2016**, *55*, 16084.

VTNA in Action



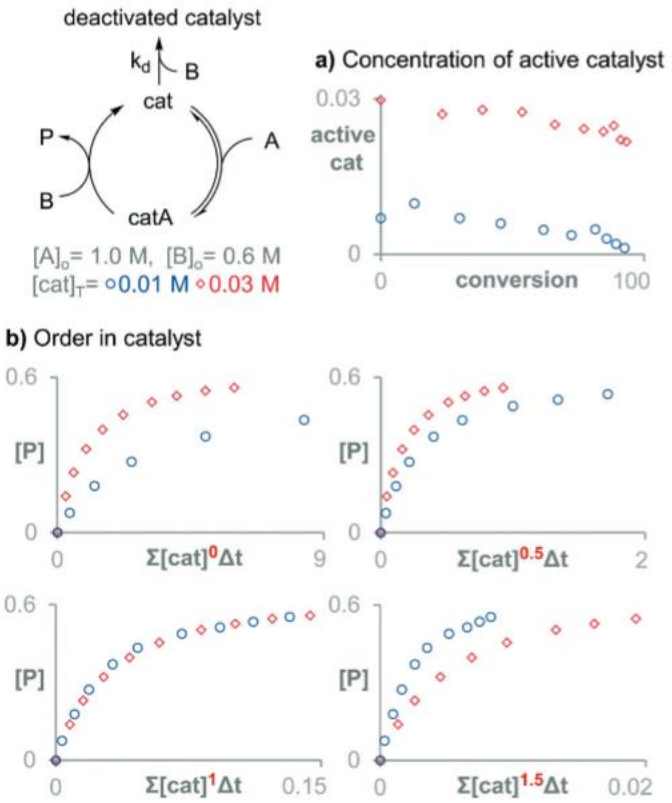
- Repeat this procedure to find order in [B] and [cat]



- **This procedure to find order in [cat] only holds if there is no catalyst deactivation (i.e. [cat] = constant during rxn)**

ACIE **2016**, *55*, 16084.

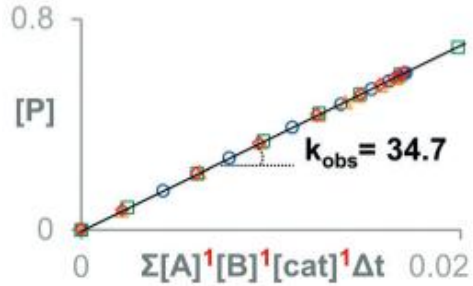
VTNA in Action – Determining Order in [Cat] with Cat. Deactivation



- Same procedure as finding reaction order in [A] or [B], but concentration of active catalyst must be measurable over time
- The method for detecting catalyst deactivation in the RPKA section can be used to see if deactivation occurs.

ACIE **2016**, *55*, 16084.

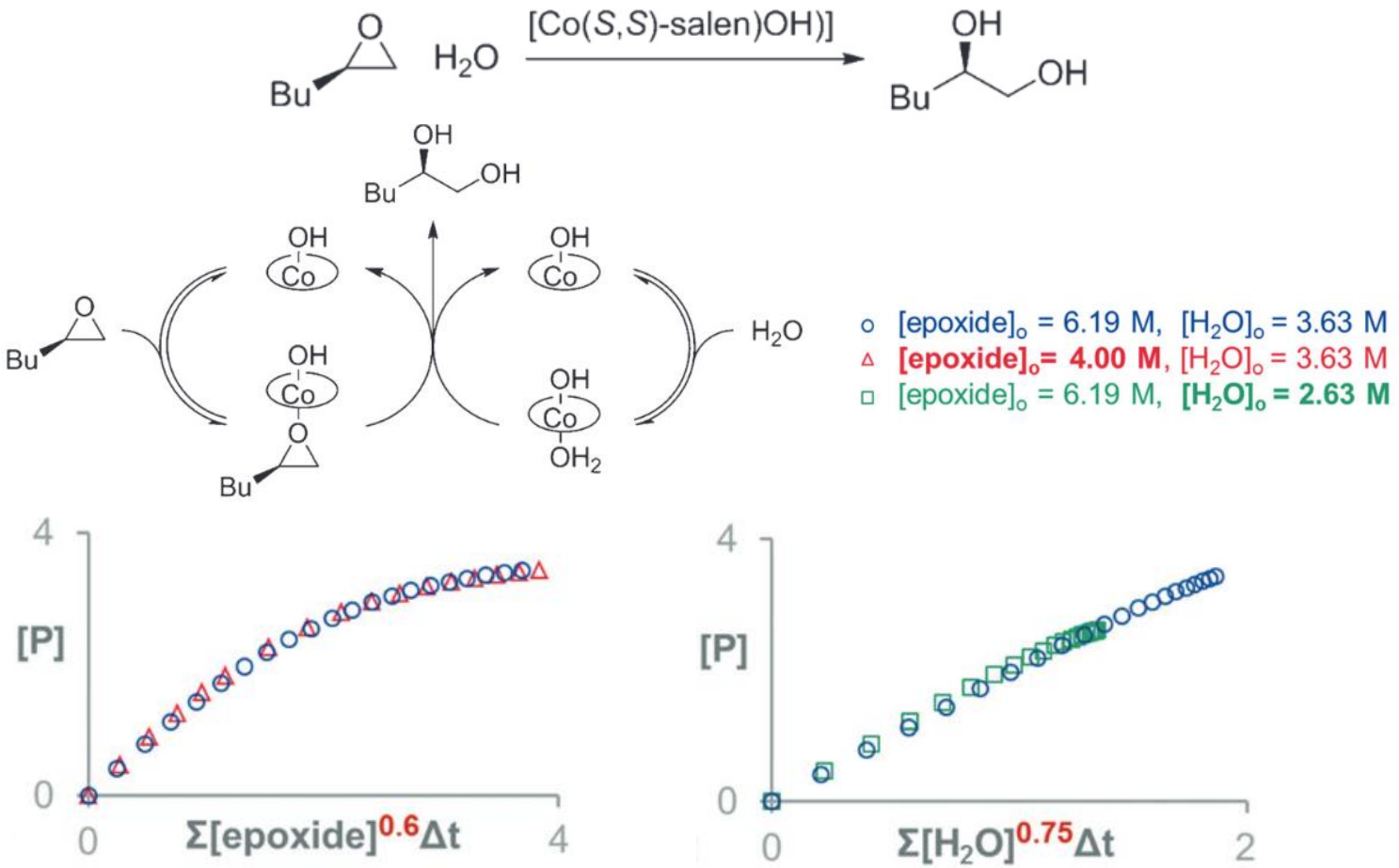
VTNA in Action



- When all components in the time normalized axis are raised to their order, a straight line is obtained with a slope = k_{obs}

ACIE **2016**, *55*, 16084.

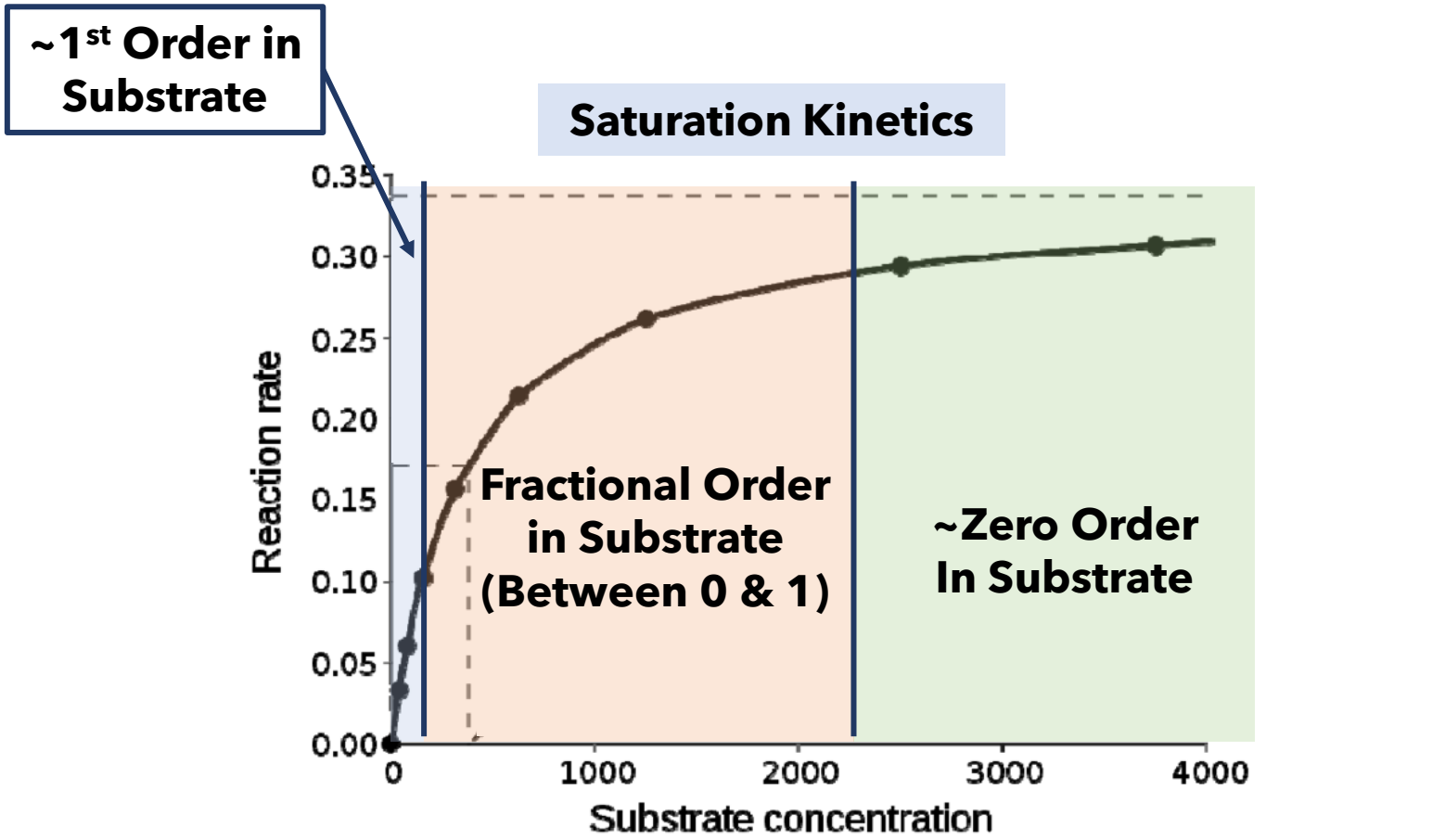
Word of Warning – Fractional Orders



- Fractional orders that are not multiples of ½ likely arise from a change in reagent order that occurs during reaction
- Here, ***average orders*** are obtained for $[H_2O]$ and [epoxide] by VTNA, in a reaction where these orders change over the course of reaction

JACS, **2013**, *135*, 15595. *ACIE* **2016**, *55*, 16084.

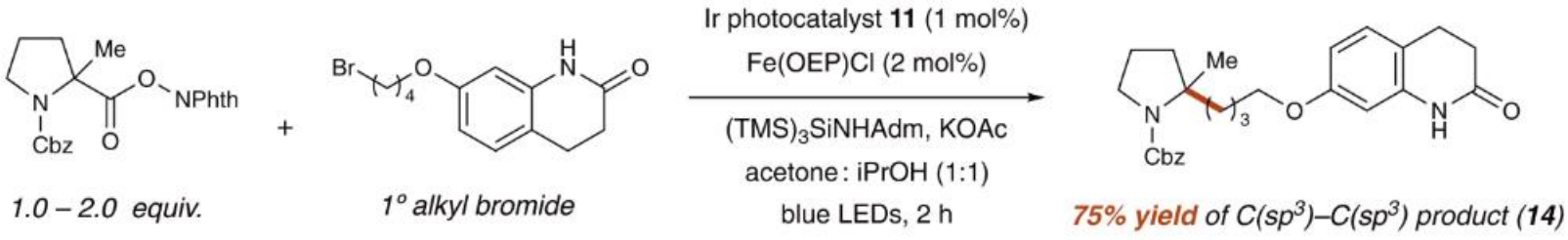
Word of Warning – Fractional Orders

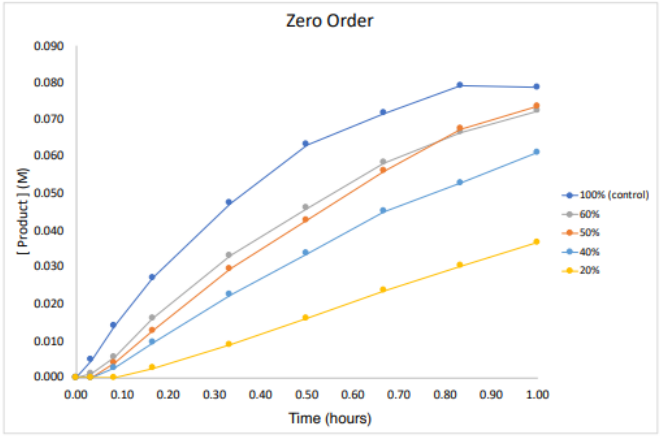


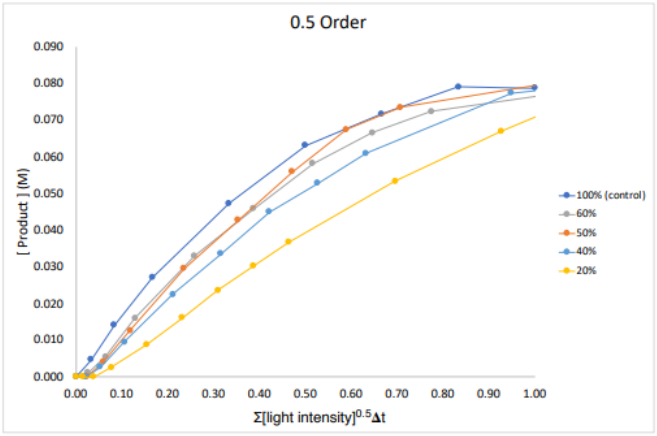
- Elucidation of non-averaged order are obtained by restricting analysis to specific "sections" of the reaction
- These sections are defined by concentration of reactants.

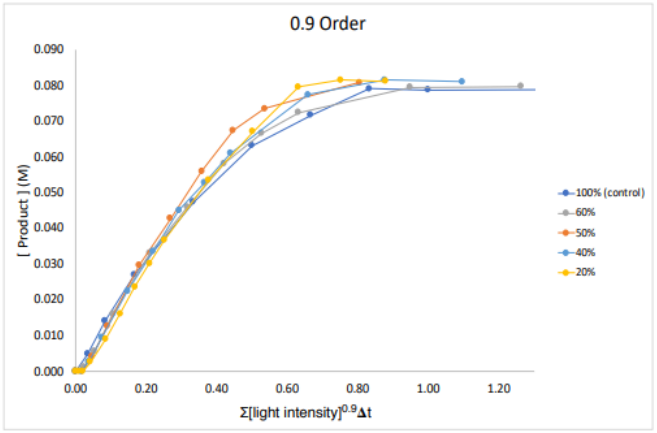
ACIE **2016**, *55*, 16084.

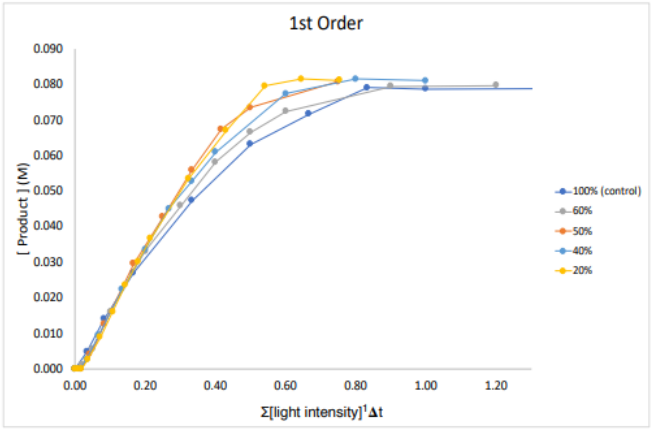
Example of VTNA in the Literature – 1st Order in Light Intensity











Science, **2021**, *374*, *1258*.

Conclusion

- RPKA and VTNA provide quick and mostly straightforward methods for determining key kinetic parameters. Reactions do not always need to be well-behaved.
- **There is a learning curve but well worth the time savings compared to canonical approaches to kinetics**
- Likely to supplant more classical methods in the future
- VTNA is more accessible instrumentation wise and can do much of what RPKA can
- VTNA is the spiritual successor of RPKA, and knowledge of RPKA and its use in past studies will still be useful in the application of VTNA