

An Introduction to Kinetics and Competition Experiments:

Part 1 – Absolute Rates

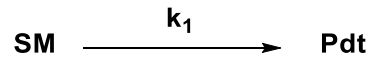
Daniel Strassfeld

Yu lab

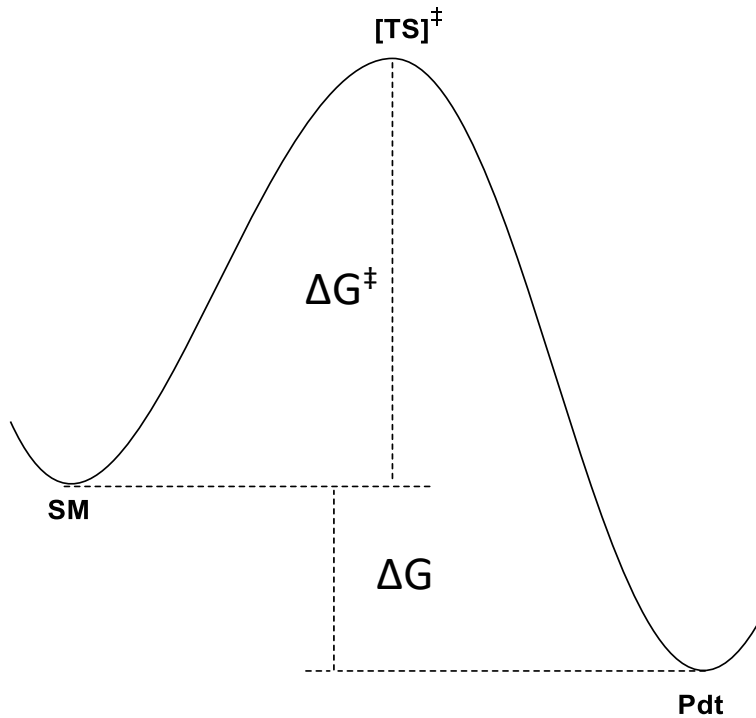
Literature talk – 7/12/21

A brief introduction to transition state theory

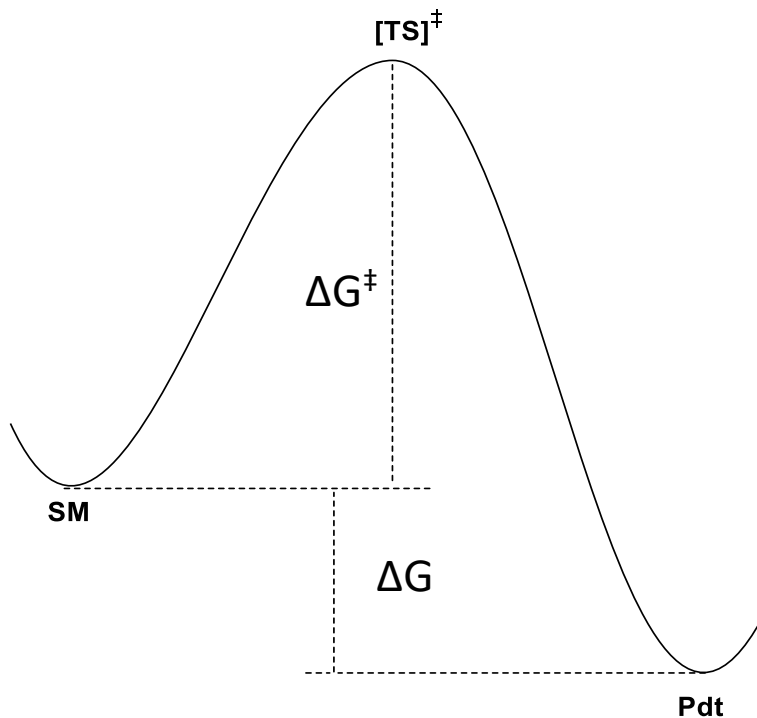
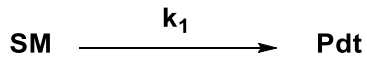
1) Reaction rate is proportional to $[TS]^\ddagger$



$$\frac{-d[SM]}{dt} \propto [TS]^\ddagger$$



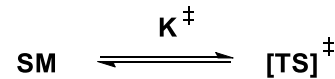
A brief introduction to transition state theory



1) Reaction rate is proportional to $[\text{TS}]^\ddagger$

$$\frac{-d[\text{SM}]}{dt} \propto [\text{TS}]^\ddagger$$

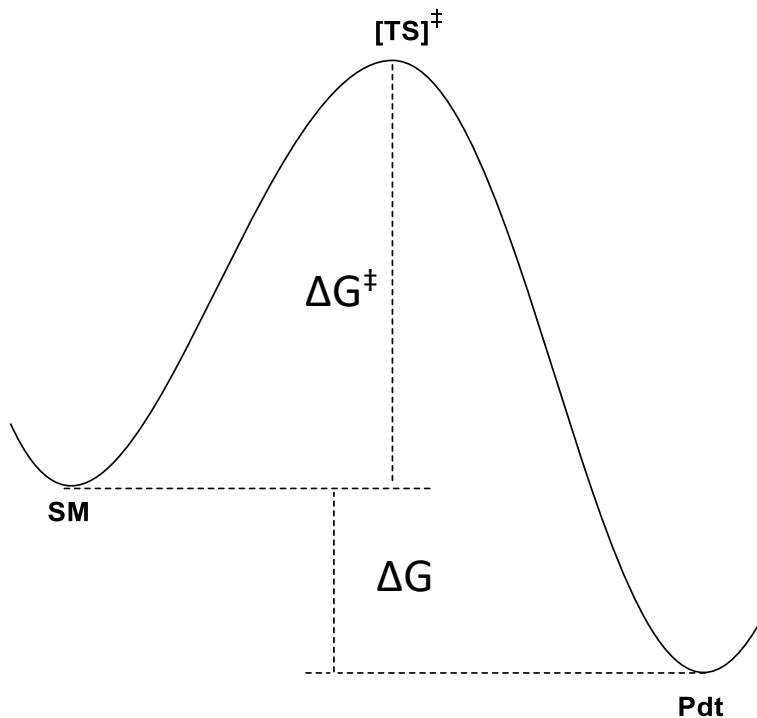
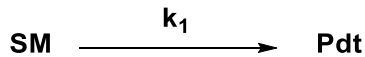
2) Assume a “quasi-equilibrium” between the resting state and the transition state



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{SM}]}$$

$$K^\ddagger = e^{-\Delta G^\ddagger/RT}$$

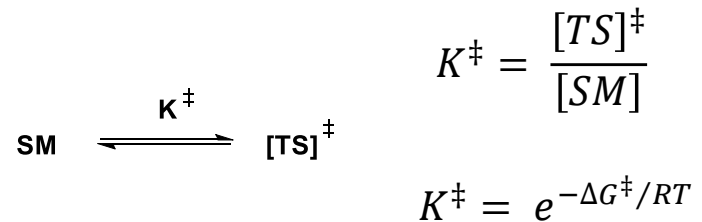
A brief introduction to transition state theory



1) Reaction rate is proportional to $[TS]^\ddagger$

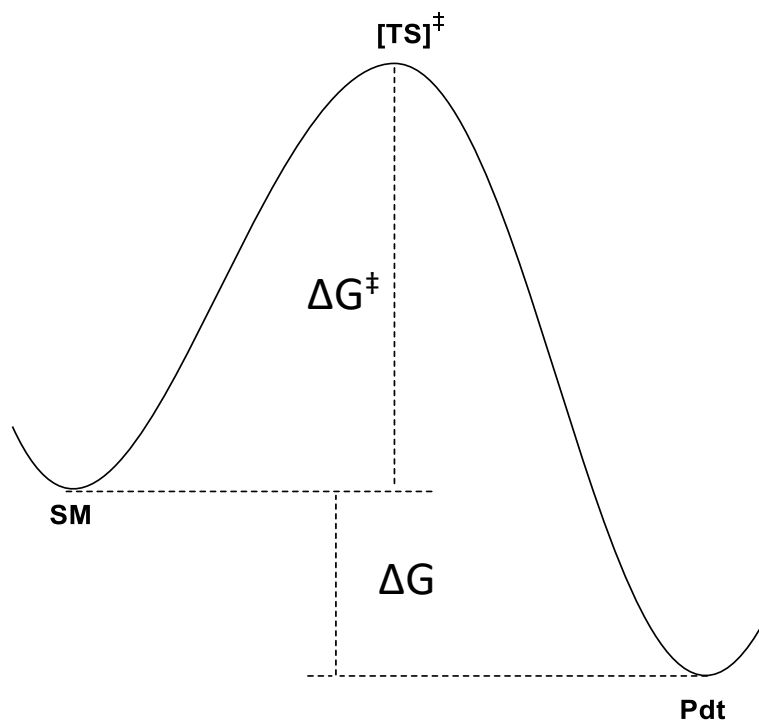
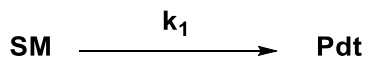
$$\frac{-d[SM]}{dt} \propto [TS]^\ddagger$$

2) Assume a “quasi-equilibrium” between the resting state and the transition state



$$\frac{-d[SM]}{dt} \propto e^{-\Delta G^\ddagger/RT} [SM]$$

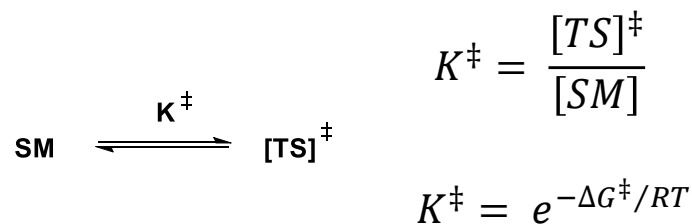
A brief introduction to transition state theory



1) Reaction rate is proportional to $[TS]^\ddagger$

$$\frac{-d[SM]}{dt} \propto [TS]^\ddagger$$

2) Assume a “quasi-equilibrium” between the resting state and the transition state



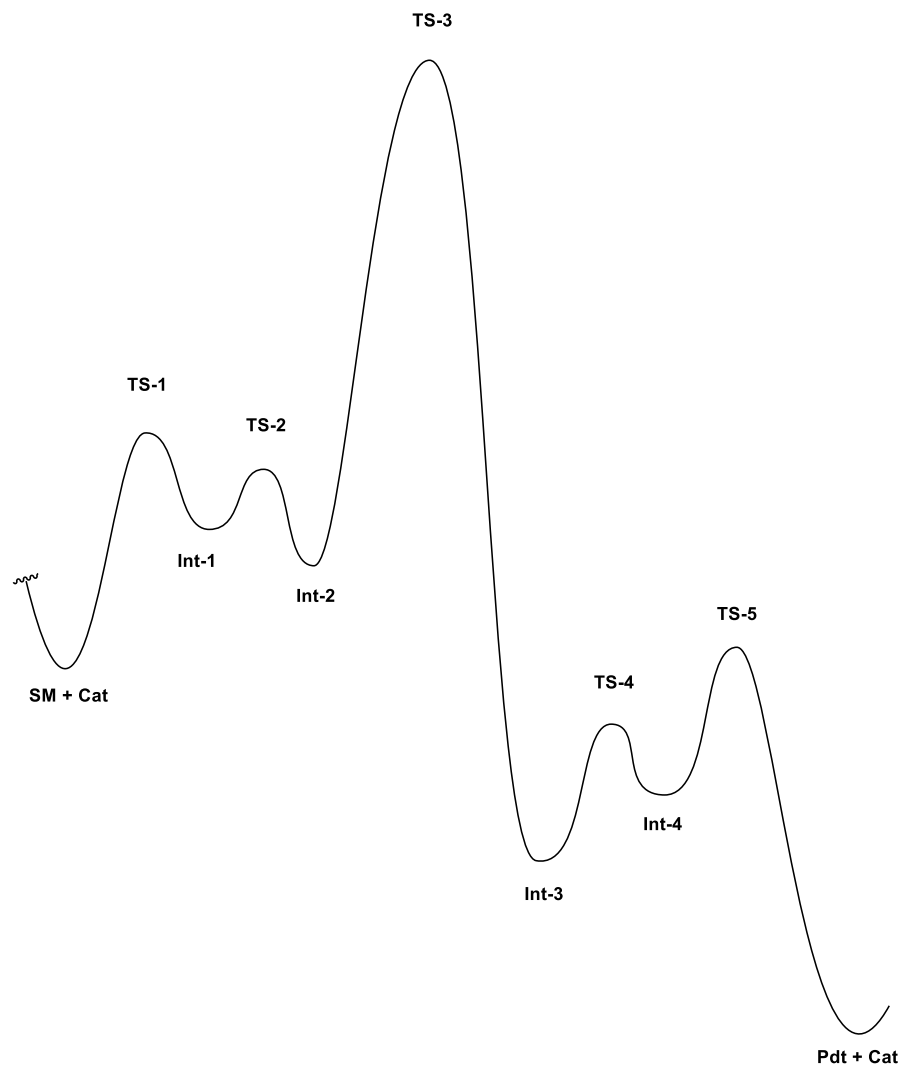
$$\frac{-d[SM]}{dt} \propto e^{-\Delta G^\ddagger/RT} [SM]$$

Transmission coefficient
(usually assumed to be 1)

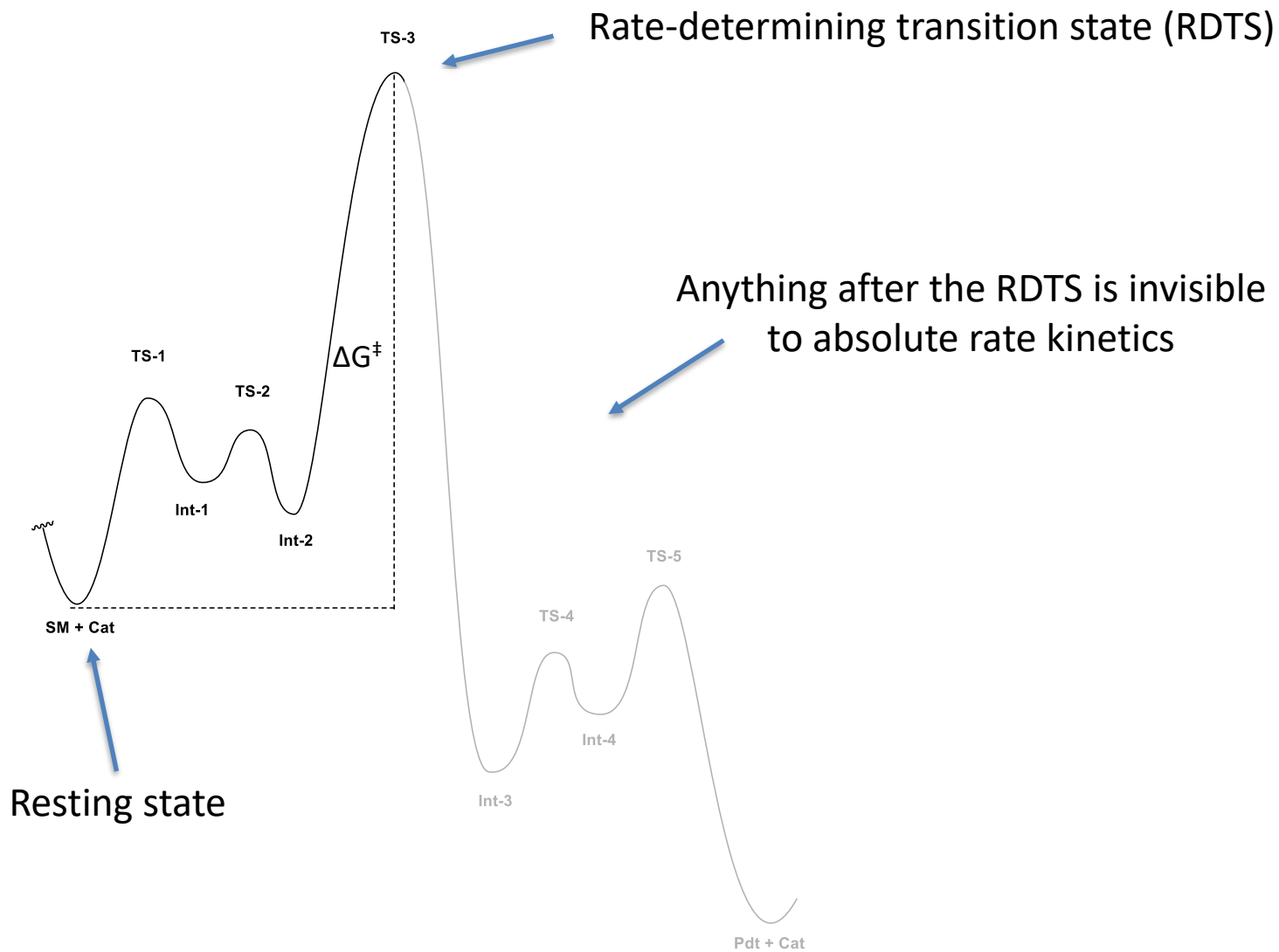
Crossing frequency
(from stat mech)

$$\frac{-d[SM]}{dt} = \underbrace{\kappa * \frac{k_B T}{h} * e^{-\Delta G^\ddagger/RT}}_{\text{Eyring equation}} [SM]$$

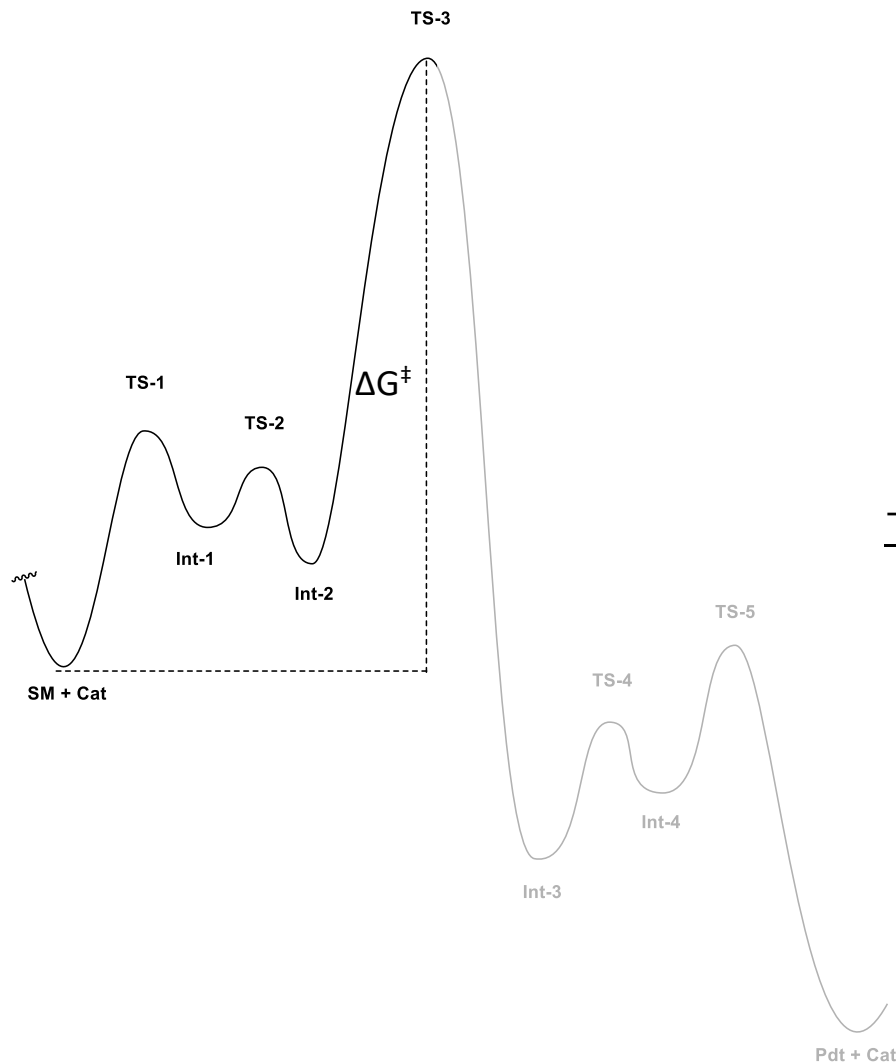
Kinetics of complex reaction coordinates



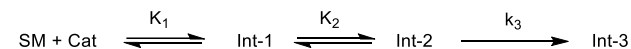
Kinetics of complex reaction coordinates – not as bad as they seem



Kinetics of complex reaction coordinates – not as bad as they seem



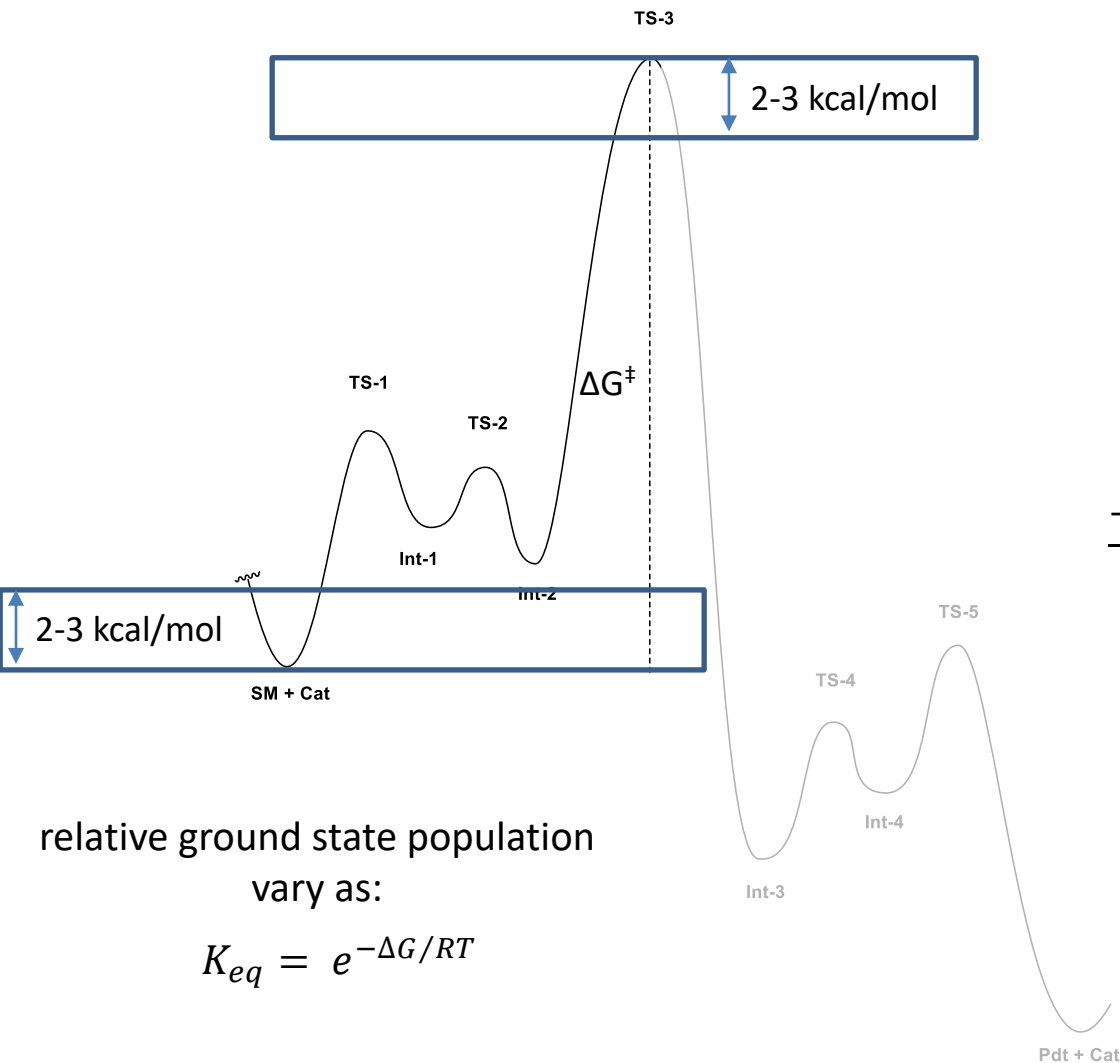
Apply the pre-equilibrium approximation, etc. ...



$$\frac{-d[\text{SM}]}{dt} \approx \frac{k_3 * K_1 * K_2 * [\text{SM}] * [\text{Cat}_T]}{1 + K_1 * [\text{SM}] + K_1 * K_2 * [\text{SM}]}$$

Approximate because I'm assuming a negligible amount of catalyst is tied up in the post-rate-determining intermediates

Kinetics of complex reaction coordinates – really not as bad as they seem



relative rates vary as:

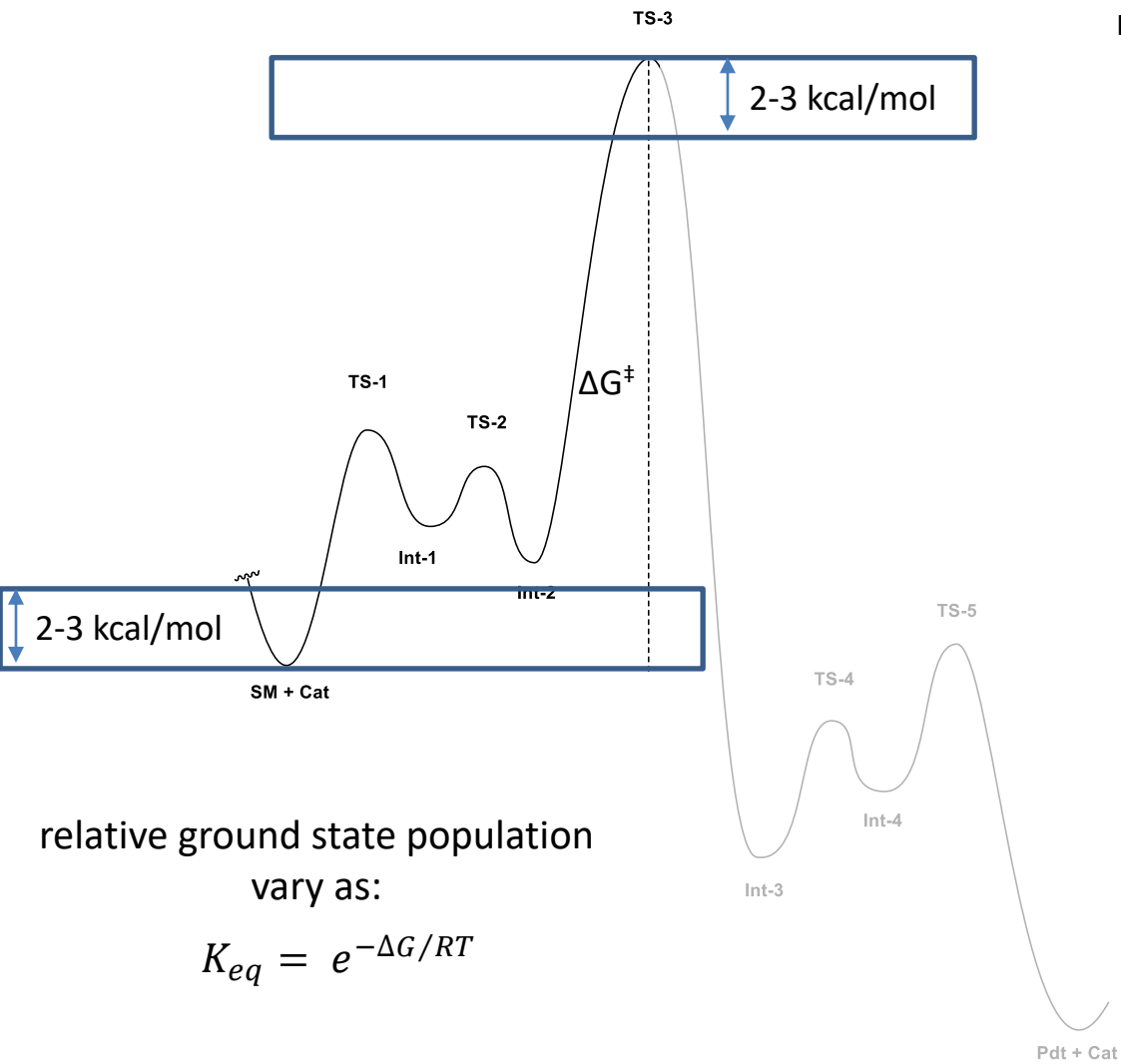
$$K^\ddagger = e^{-\Delta G^\ddagger/RT}$$

Unless another barrier is close to the RDTS, $k_3 * K_1 * K_2$ will be approximated by ΔG^\ddagger

$$\frac{-d[SM]}{dt} \approx \frac{k_3 * K_1 * K_2 * [SM] * [Cat_T]}{1 + K_1 * [SM] + K_1 * K_2 * [SM]}$$

Unless the intermediates are close in energy to the resting state, these terms are negligible

Kinetics of complex reaction coordinates – really not as bad as they seem



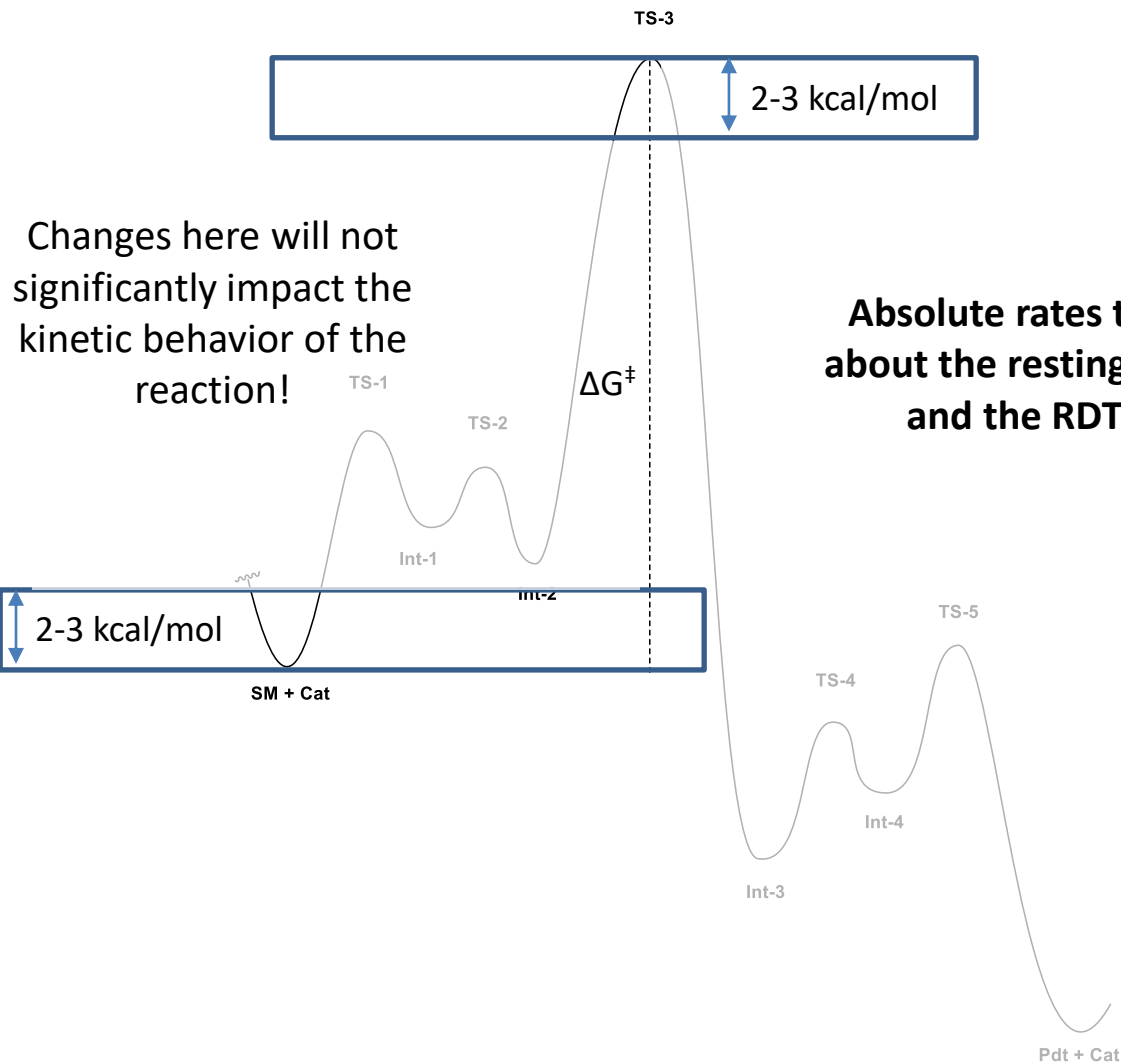
relative rates vary as:

$$K^\ddagger = e^{-\Delta G^\ddagger/RT}$$

$\Delta G = 2.5$ kcal/mol:

Temp	$e^{-\Delta G/RT}$
100 °C	29 : 1
25 °C	68 : 1
-78 °C	631 : 1

Kinetics of complex reaction coordinates – really not as bad as they seem

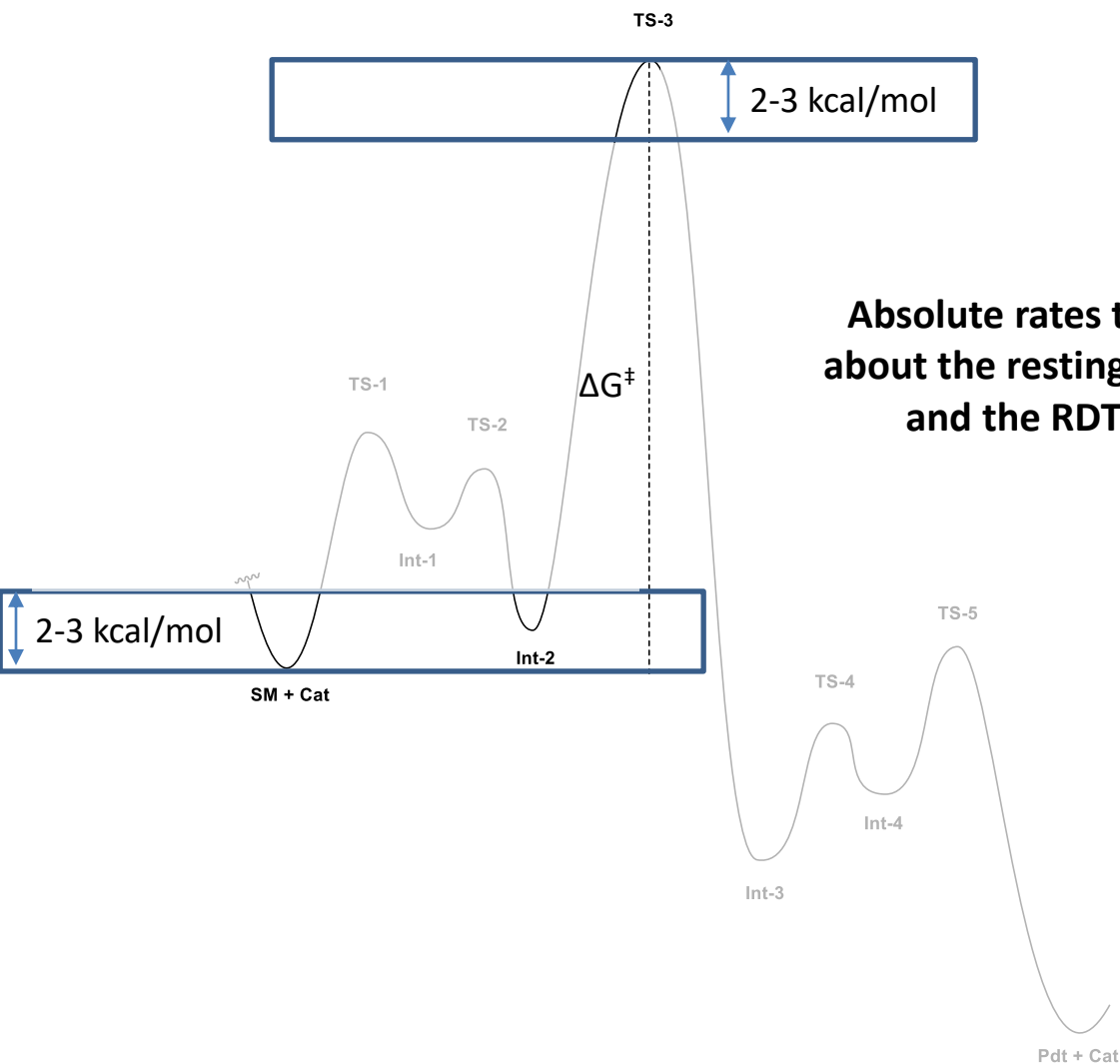


Absolute rates tell you about the resting state(s) and the RDTS(s)

$\Delta G = 2.5$ kcal/mol:

Temp	$e^{-\Delta G/RT}$
100 °C	29 : 1
25 °C	68 : 1
-78 °C	631 : 1

Kinetics of complex reaction coordinates – really not as bad as they seem (mostly)

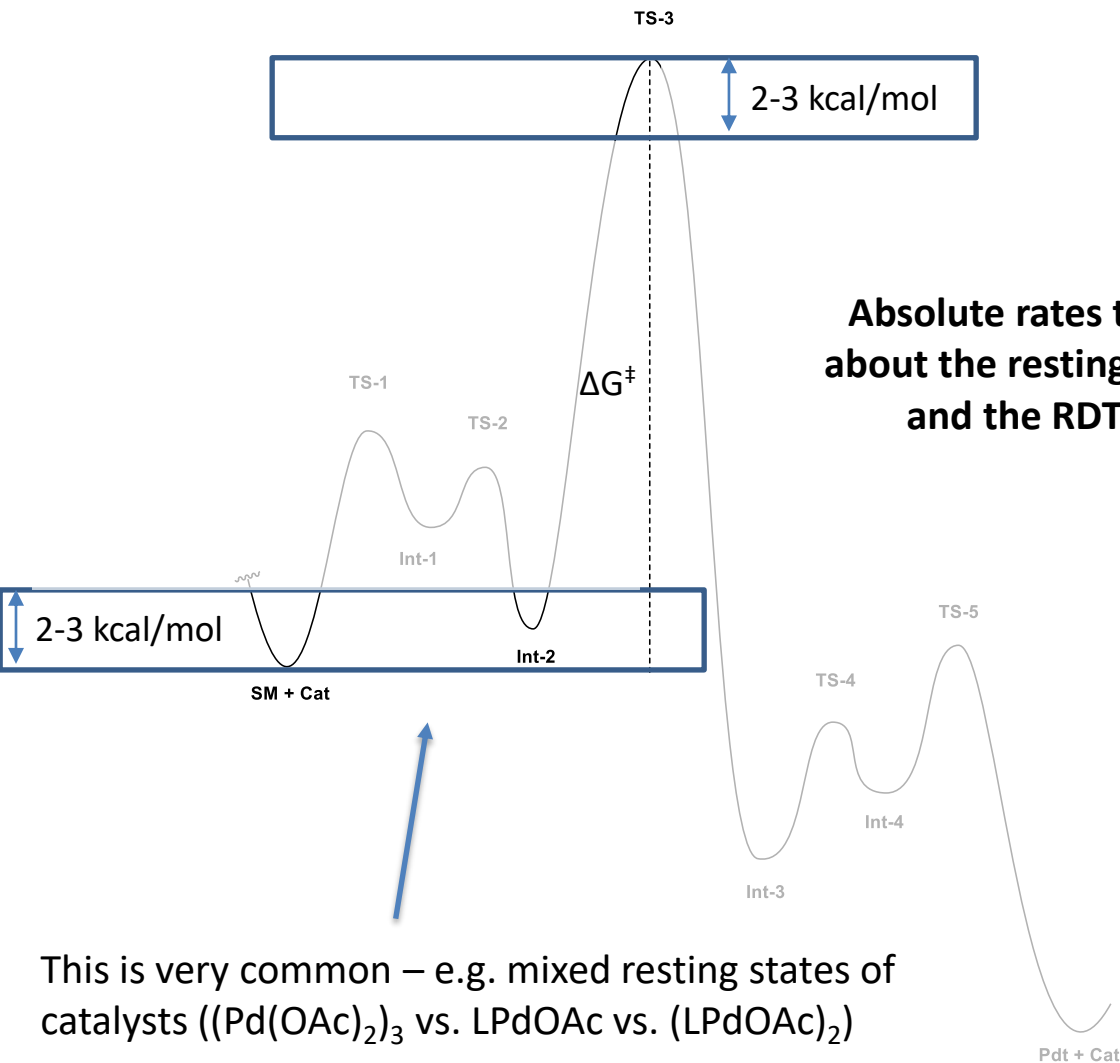


**Absolute rates tell you
about the resting state(s)
and the RDTS(s)**

$\Delta G = 2.5$ kcal/mol:

Temp	$e^{-\Delta G/RT}$
100 °C	29 : 1
25 °C	68 : 1
-78 °C	631 : 1

Kinetics of complex reaction coordinates – really not as bad as they seem (mostly)



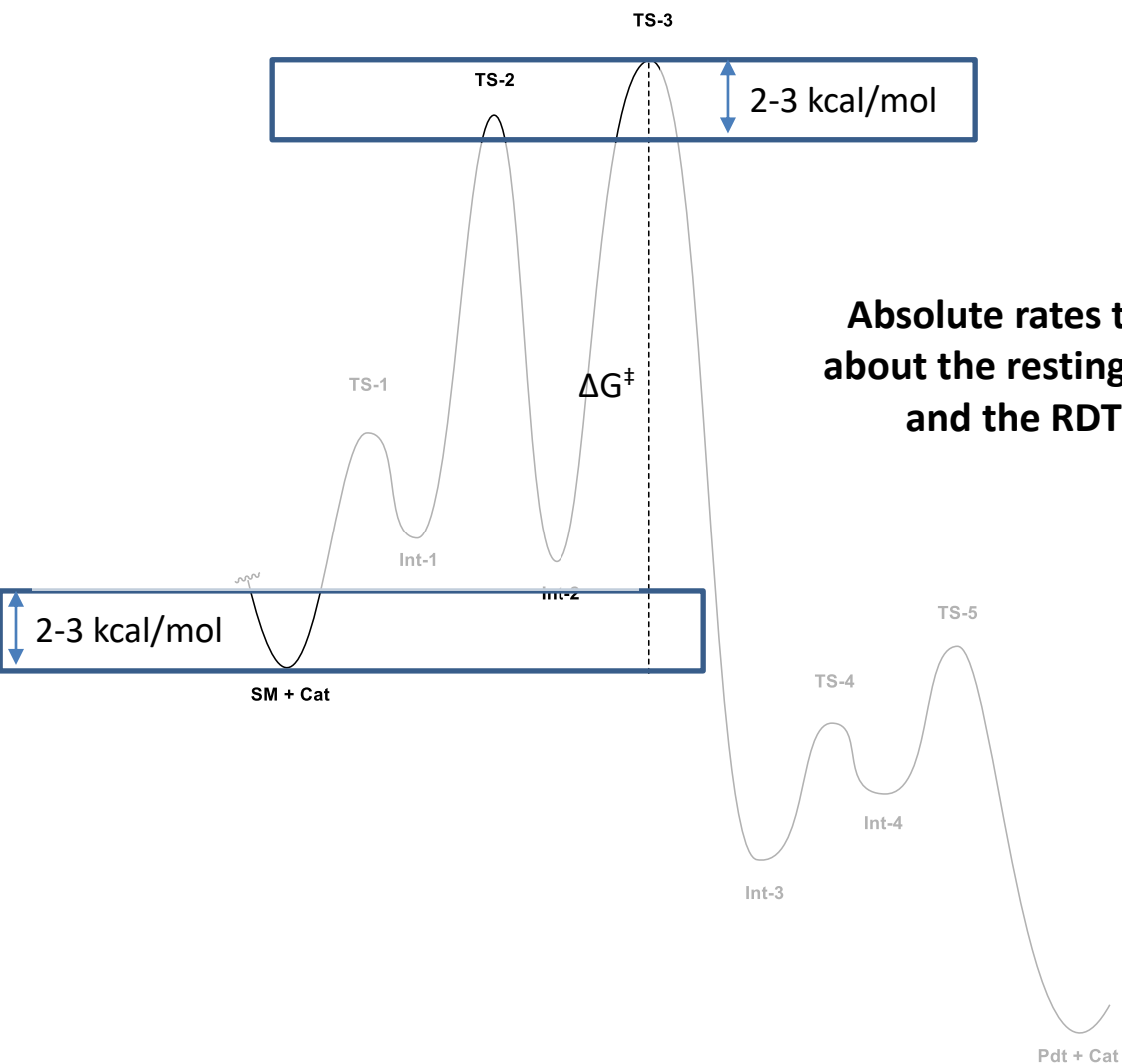
Absolute rates tell you about the resting state(s) and the RDTS(s)

ΔG = 2.5 kcal/mol:

Temp	$e^{-\Delta G/RT}$
100 °C	29 : 1
25 °C	68 : 1
-78 °C	631 : 1

This is very common – e.g. mixed resting states of catalysts ($(\text{Pd}(\text{OAc})_2)_3$ vs. LPdOAc vs. $(\text{LPdOAc})_2$)

Kinetics of complex reaction coordinates – really not as bad as they seem (mostly)

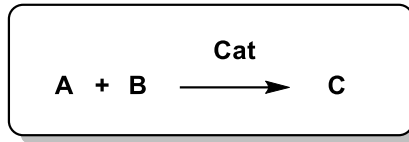


Absolute rates tell you about the resting state(s) and the RDTS(s)

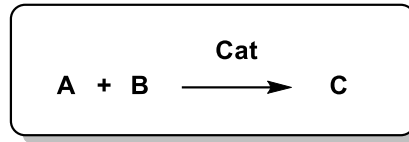
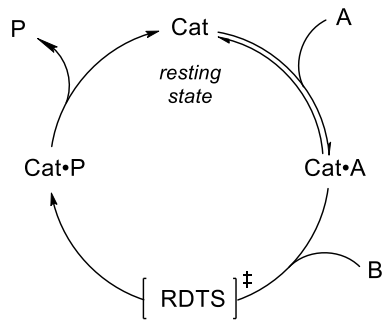
$\Delta G = 2.5$ kcal/mol:

Temp	$e^{-\Delta G/RT}$
100 °C	29 : 1
25 °C	68 : 1
-78 °C	631 : 1

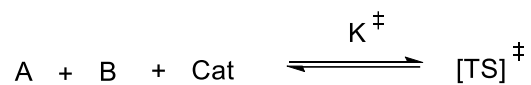
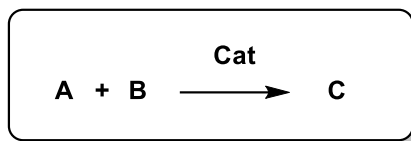
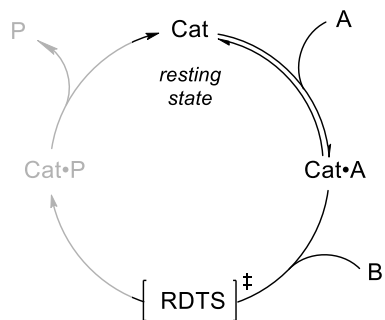
Deriving approximate rate laws for some common kinetic scenarios



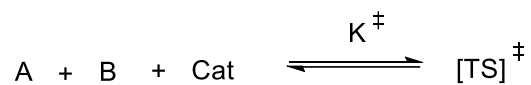
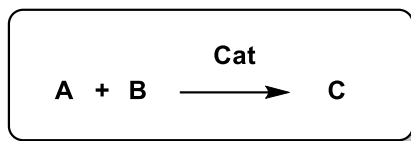
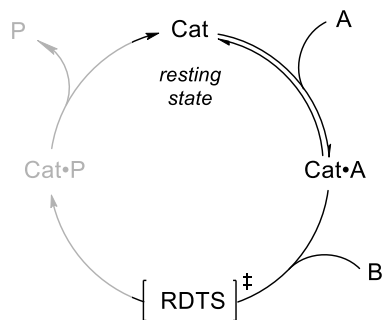
Deriving approximate rate laws for some common kinetic scenarios



Deriving approximate rate laws for some common kinetic scenarios

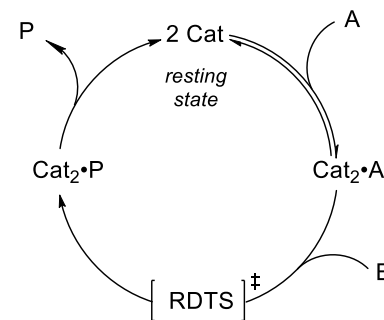
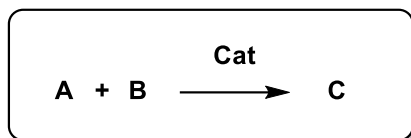
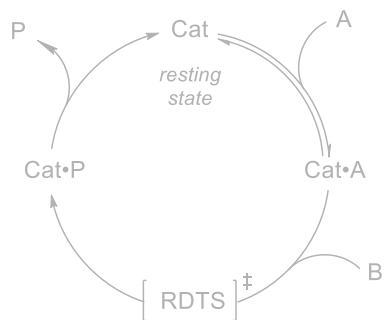


Deriving approximate rate laws for some common kinetic scenarios



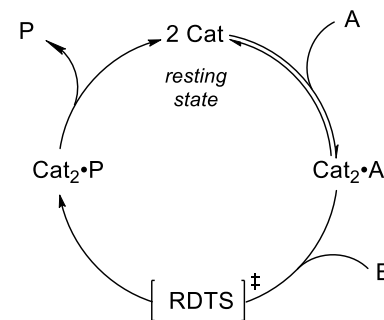
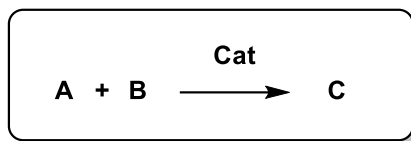
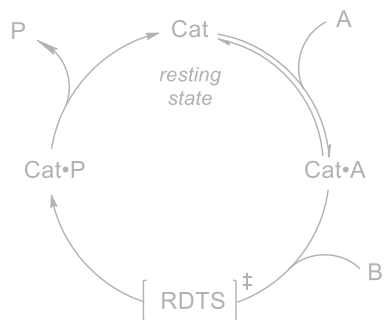
$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]$$

Deriving approximate rate laws for some common kinetic scenarios

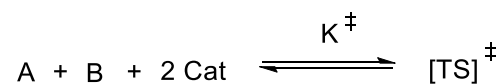


$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]$$

Deriving approximate rate laws for some common kinetic scenarios

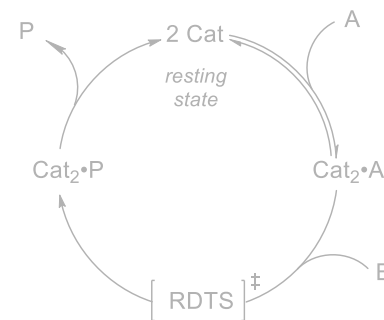
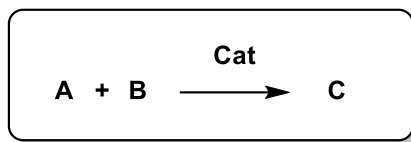
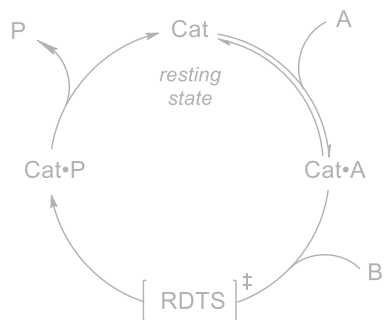


$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]^2} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]^2$$

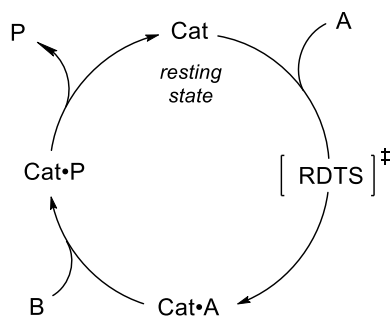
Deriving approximate rate laws for some common kinetic scenarios



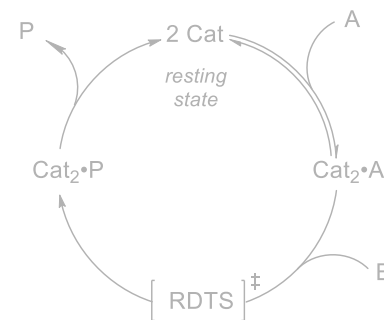
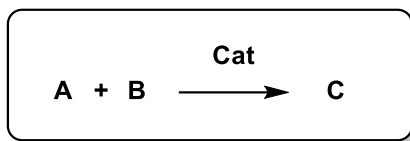
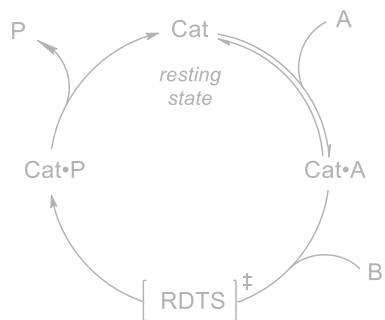
$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]^2} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]^2$$



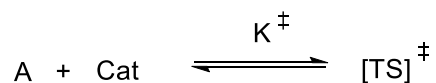
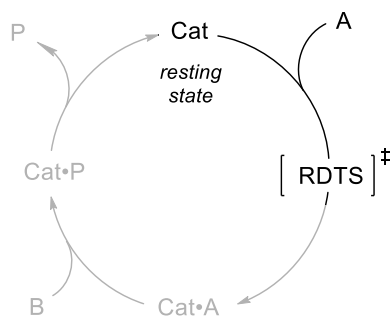
Deriving approximate rate laws for some common kinetic scenarios



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]$$

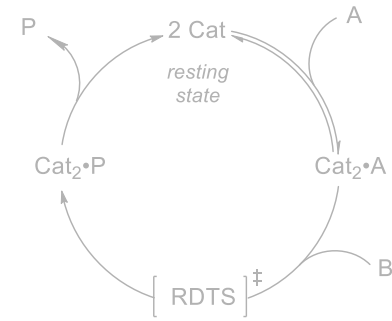
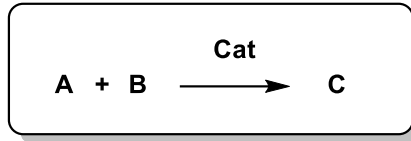
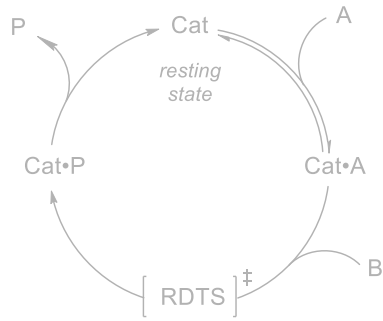


$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]^2} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]^2$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{Cat}]$$

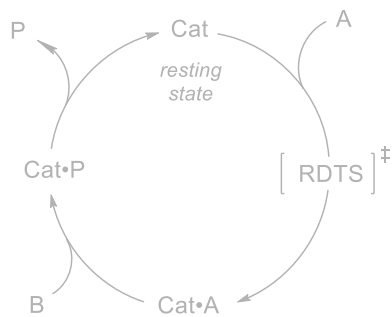
Deriving approximate rate laws for some common kinetic scenarios



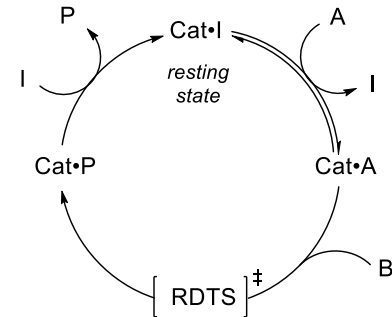
$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]$$



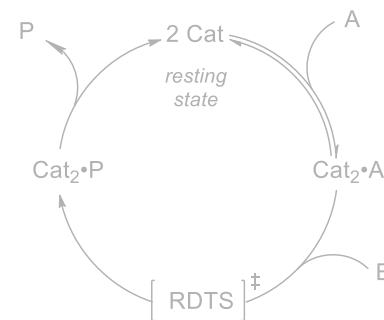
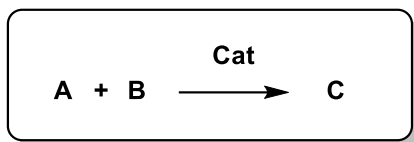
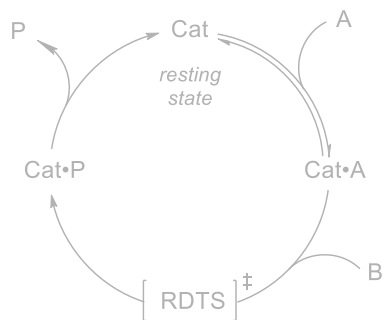
$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]^2} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]^2$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{Cat}]$$



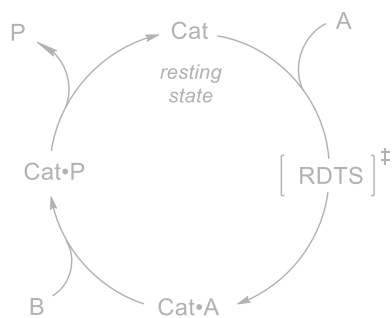
Deriving approximate rate laws for some common kinetic scenarios



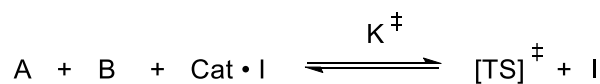
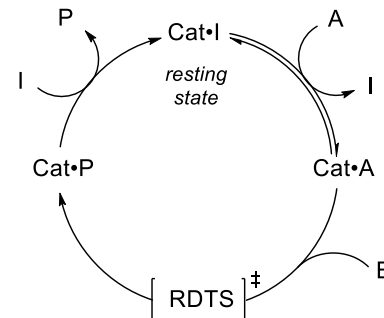
$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{B}] * [\text{Cat}]^2} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat}]^2$$

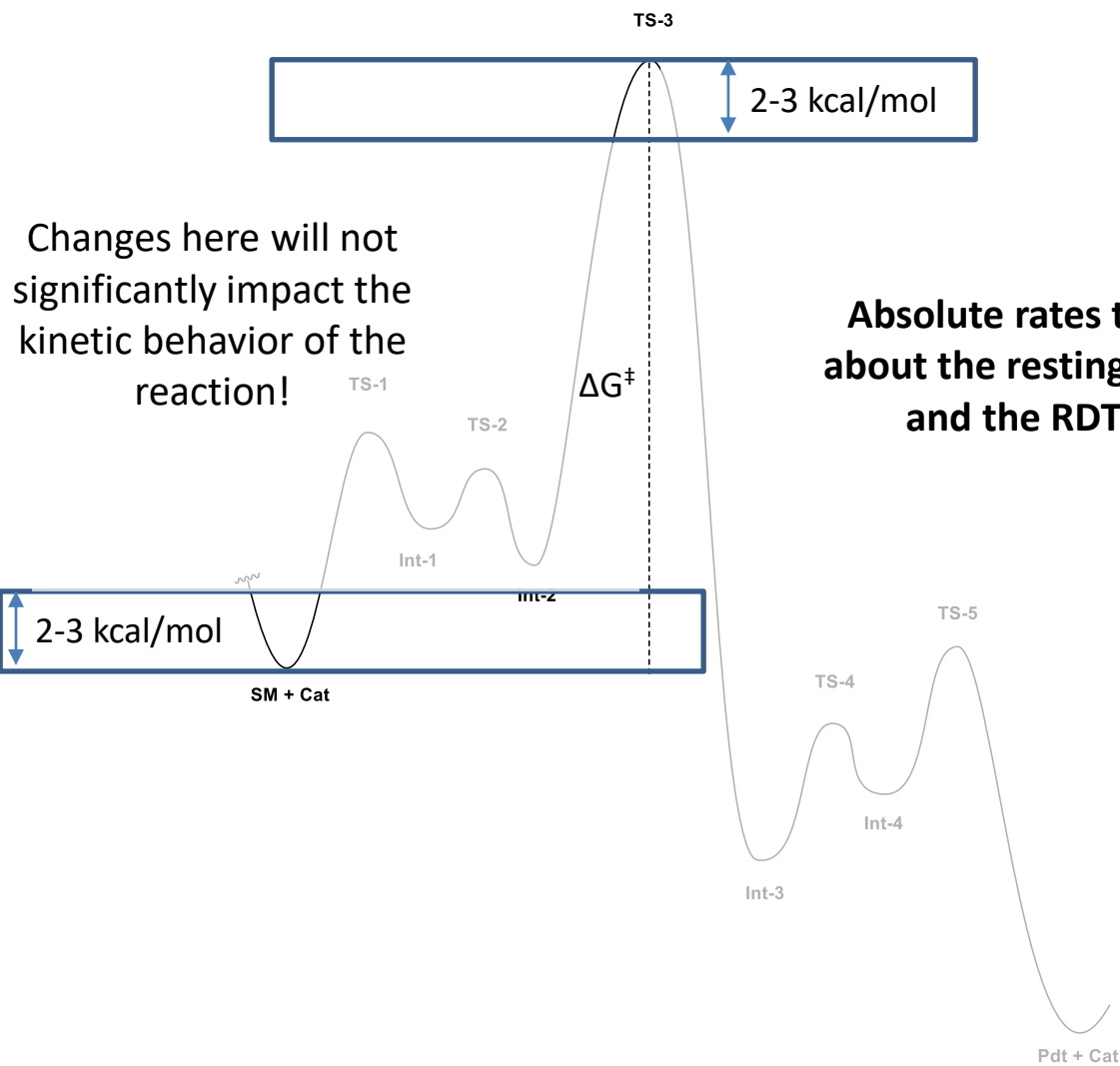


$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[\text{A}] * [\text{Cat}]} \quad \text{rate} \propto [\text{A}] * [\text{Cat}]$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger * [\text{I}]}{[\text{A}] * [\text{B}] * [\text{Cat} \cdot \text{I}]} \quad \text{rate} \propto [\text{A}] * [\text{B}] * [\text{Cat} \cdot \text{I}] * [\text{I}]^{-1}$$

If absolute rates only tell you about the resting state(s) and the RDTs, then why bother?



Absolute rates tell you about the resting state(s) and the RDTs(s)



Ok, but who cares?

If absolute rates only tell you about the resting state(s) and the RDTs, then why bother?

1) Determining the kinetic order in a reagent or reagents

- determine the presence/absence/molecularity of a species in the RDTs
 - help to support/refute a proposal for the identity of the RDTs
 - help guide other mechanistic studies (e.g. computations)

If absolute rates only tell you about the resting state(s) and the RDTS, then why bother?

1) Determining the kinetic order in a reagent or reagents

- determine the presence/absence/molecularity of a species in the RDTS
 - help to support/refute a proposal for the identity of the RDTS
 - help guide other mechanistic studies (e.g. computations)

2) Examine how the rate law changes over the reaction

- Identify induction periods
- Identify catalyst deactivation

If absolute rates only tell you about the resting state(s) and the RDTS, then why bother?

1) Determining the kinetic order in a reagent or reagents

- determine the presence/absence/molecularity of a species in the RDTS
 - help to support/refute a proposal for the identity of the RDTS
 - help guide other mechanistic studies (e.g. computations)

2) Examine how the rate law changes over the reaction

- Identify induction periods
- Identify catalyst deactivation

3) Identify changes in bonding or charge between the resting state and RDTS

- Separate-pot KIE experiments
- LFERs (e.g. Hammett plots)

If absolute rates only tell you about the resting state(s) and the RDTS, then why bother?

1) Determining the kinetic order in a reagent or reagents

- determine the presence/absence/molecularity of a species in the RDTS
 - help to support/refute a proposal for the identity of the RDTS
 - help guide other mechanistic studies (e.g. computations)

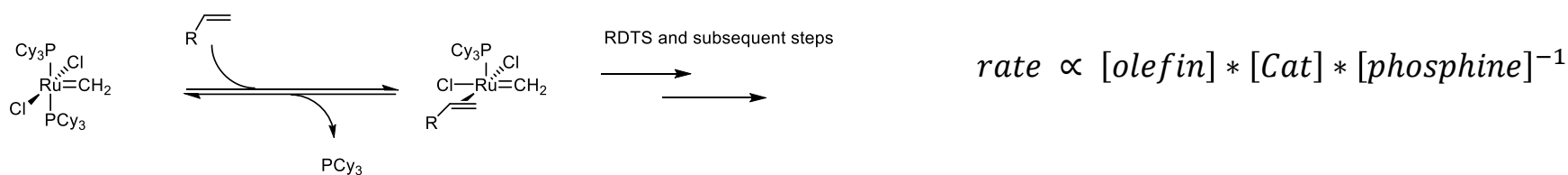
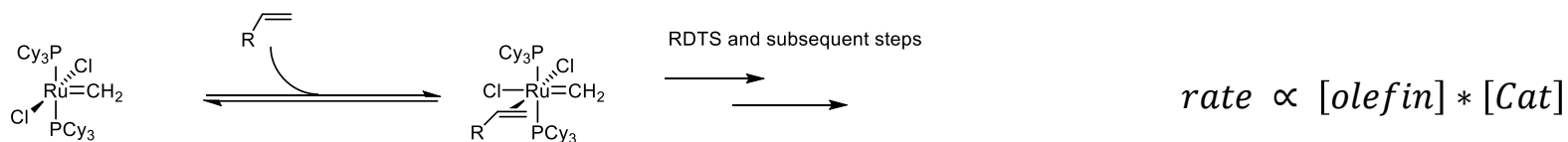
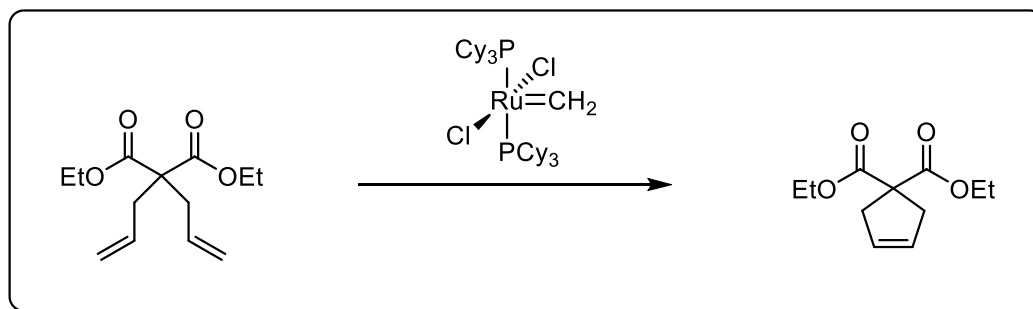
2) Examine how the rate law changes over the reaction

- Identify induction periods
- Identify catalyst deactivation

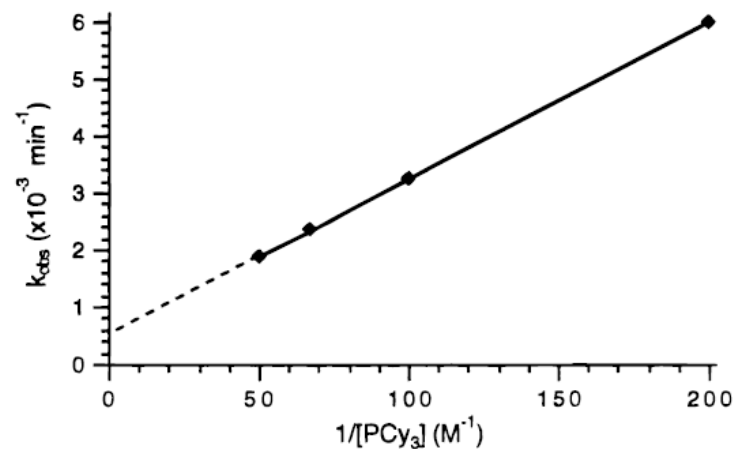
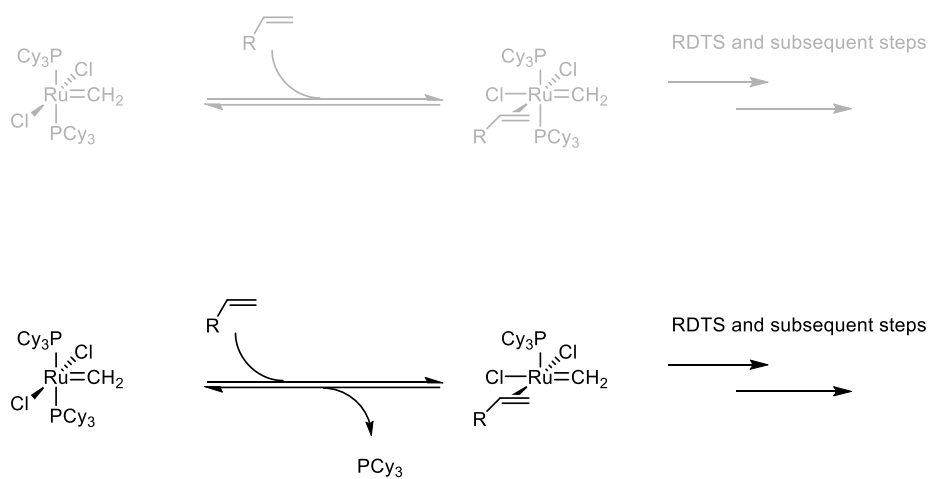
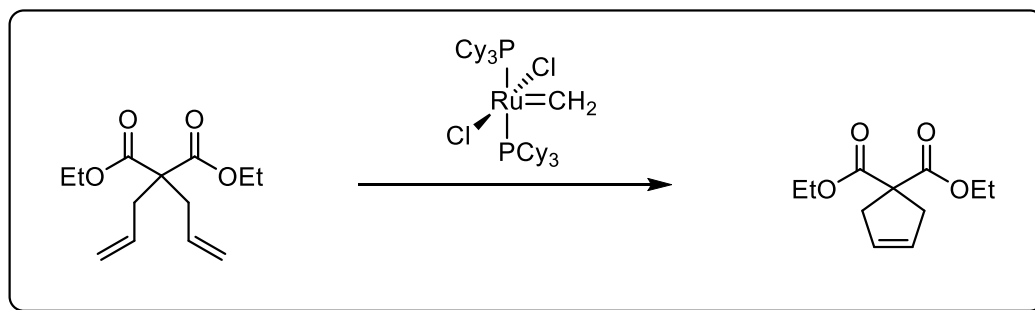
3) Identify changes in bonding or charge between the resting state and RDTS

- Separate-pot KIE experiments
- LFERs (e.g. Hammett plots)

Discovery of an inverse order in phosphine guides catalyst development for metathesis

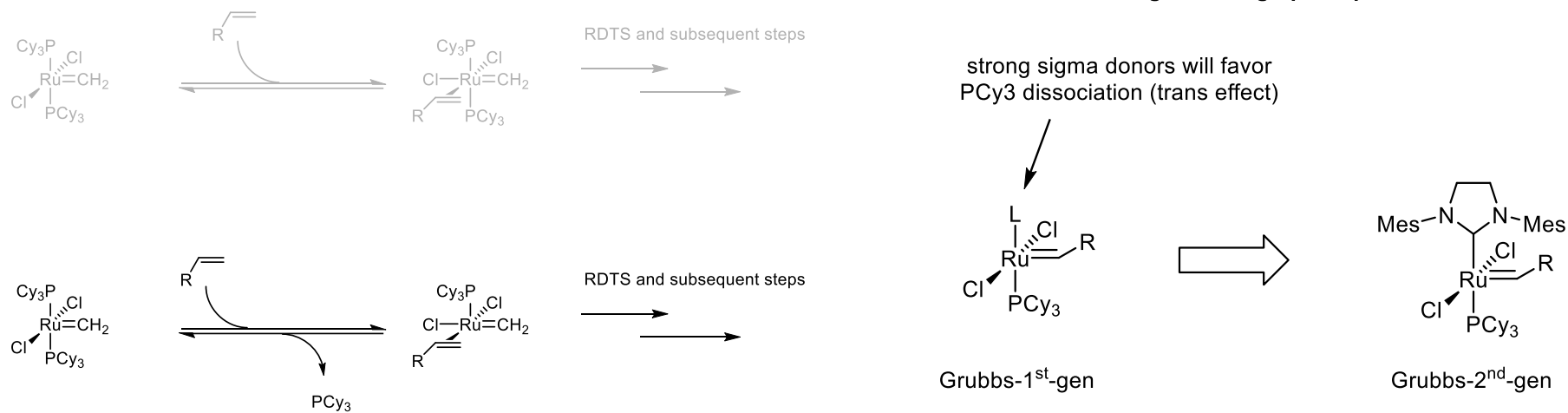
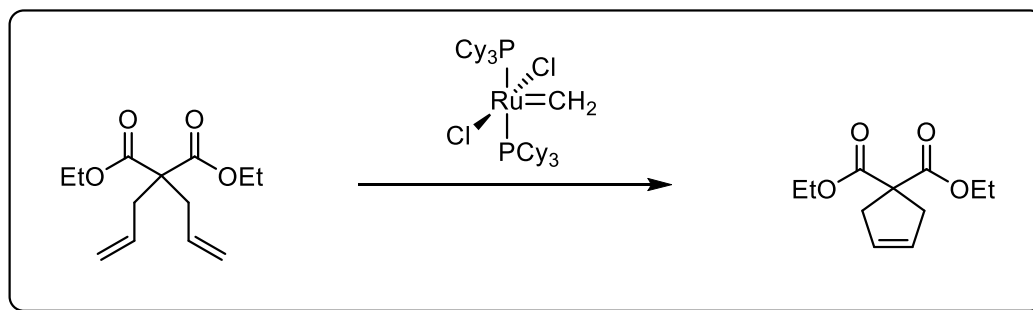


Discovery of an inverse order in phosphine guides catalyst development for metathesis

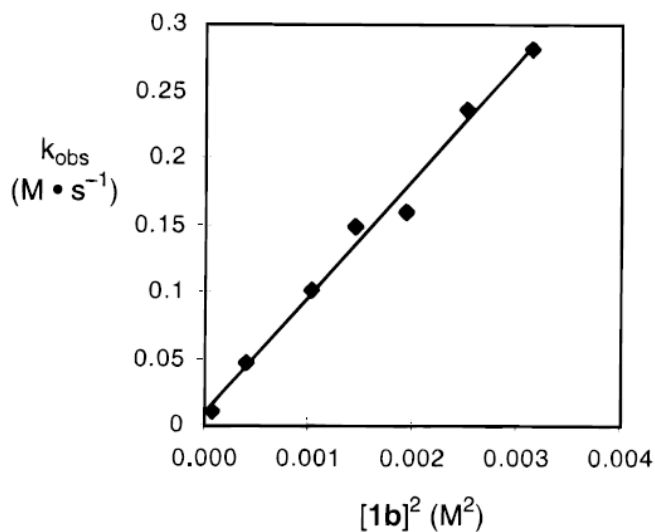
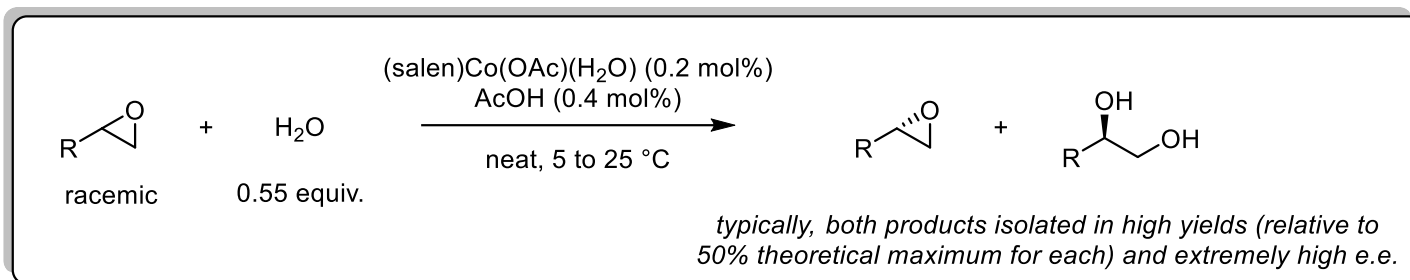


Inverse order in phosphine

Discovery of an inverse order in phosphine guides catalyst development for metathesis



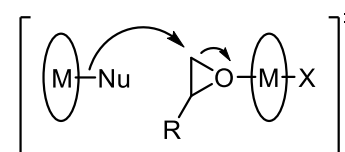
Identification of a bimetallic mechanism allows for dramatic improvement in (salen)M epoxide openings



Reaction is 2nd
order in catalyst

****These data are for (salen)Cr(III) catalyzed epoxide openings with HN₃. The HKR is also second order in catalyst, but the reaction isn't kinetically well behaved (...more on that in a bit)*

2nd order dependence on [Cat]
→ cooperative, bimetallic mechanism

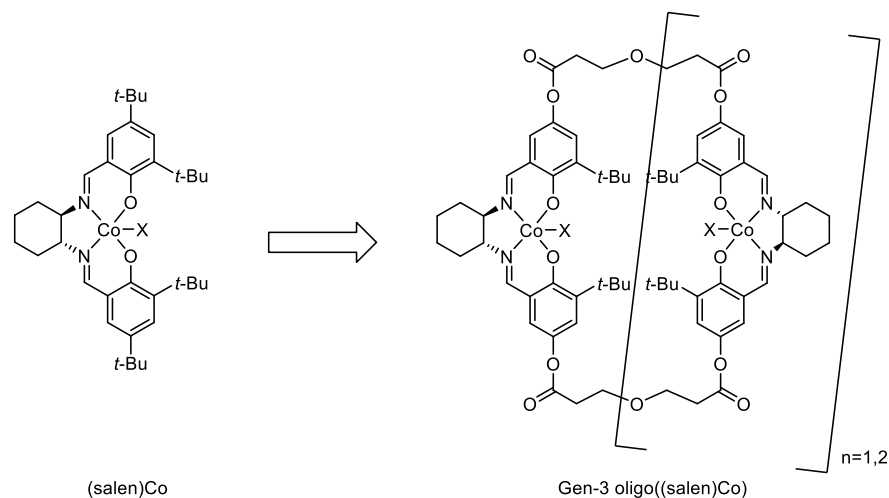
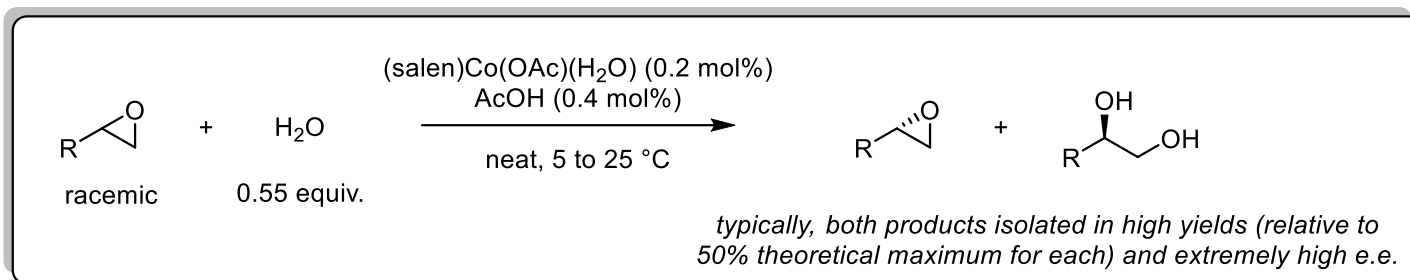


Discovery of a 2nd order dependence on [Cat] in the HKR: Jacobsen *Science* **1997**, 277, 956;

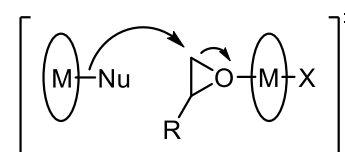
Development of oligo-salen: Jacobsen *ACIE* **2002**, 41, 1374; *Tetrahedron* **2014**, 70, 4165.

Studies on ((salen)Cr^{III})₂-catalyzed epoxide openings with azide: Jacobsen *JACS* **1996**, 118, 10924; **1998**, 120, 10780

Identification of a bimetallic mechanism allows for dramatic improvement in (salen)M epoxide openings



2^{nd} order dependence on [Cat]
→ cooperative, bimetallic mechanism

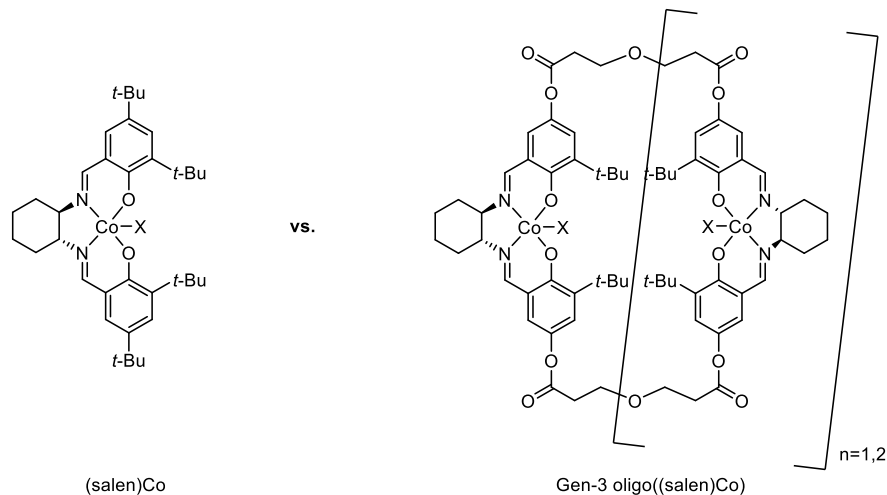


Discovery of a 2^{nd} order dependence on [Cat] in the HKR: Jacobsen *Science* **1997**, 277, 956;

Development of oligo-salen: Jacobsen *ACIE* **2002**, 41, 1374; *Tetrahedron* **2014**, 70, 4165.

Studies on $((\text{salen})\text{Cr}^{\text{III}})_2$ -catalyzed epoxide openings with azide: Jacobsen *JACS* **1996**, 118, 10924; **1998**, 120, 10780

Identification of a bimetallic mechanism allows for dramatic improvement in (salen)M epoxide openings



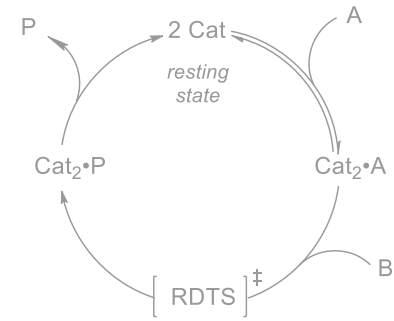
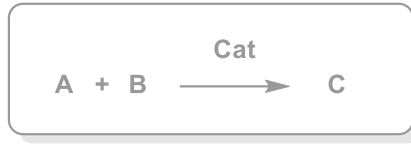
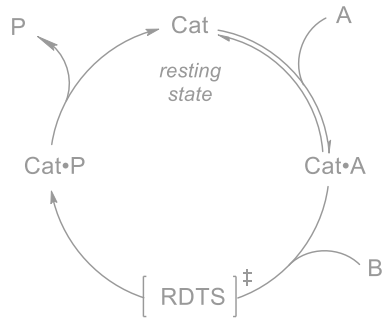
Electrophile	Nucleophile	Monomer 1 viable?	Co loading reduction with oligomer 4a ^a	Enhanced stereoselectivity or substrate scope with oligomer 4a ? ^a
Terminal epoxides	Water	Yes	22–667-fold ^b	Yes
	Carbamates	Yes	22-fold ^c	n.d. ^d
Oxetanes	Intramolecular primary alcohols	Yes	100-fold ^e	Yes
	Intramolecular phenols	Yes	10–500-fold ^e	No
Terminal epoxides	Phenols	Substrate-dependent	59–587-fold ^f	Yes
Terminal epoxides	Primary alcohols	No	—	—
meso Epoxides	Water	No	—	—
	Carbamates	No	—	—

Discovery of a 2nd order dependence on [Cat] in the HKR: Jacobsen *Science* **1997**, 277, 956;

Development of oligo-salen: Jacobsen *ACIE* **2002**, 41, 1374; *Tetrahedron* **2014**, 70, 4165.

Studies on ((salen)Cr^{III})₂-catalyzed epoxide openings with azide: Jacobsen *JACS* **1996**, 118, 10924; **1998**, 120, 10780

1 isn't always the loneliest number – higher molecularity species with 1st order dependencies



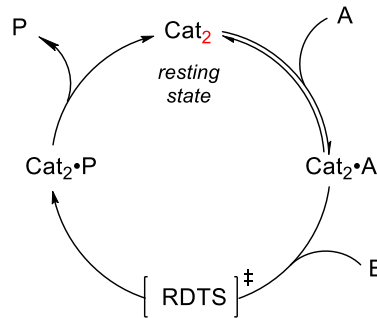
$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [B] * [\text{Cat}]}$$

$$\text{rate} \propto [A] * [B] * [\text{Cat}]$$

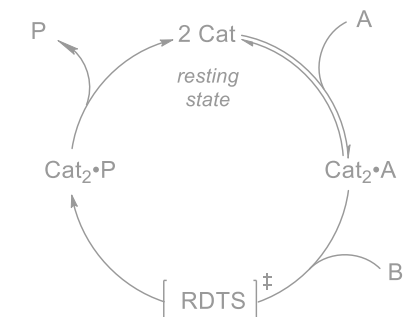
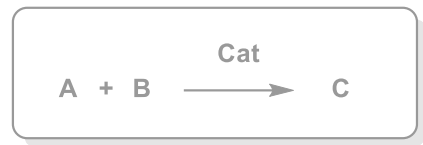
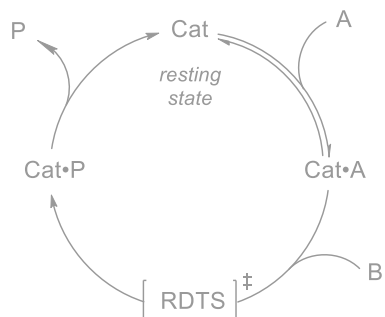


$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [B] * [\text{Cat}]^2}$$

$$\text{rate} \propto [A] * [B] * [\text{Cat}]^2$$



1 isn't always the loneliest number – higher molecularity species with 1st order dependencies



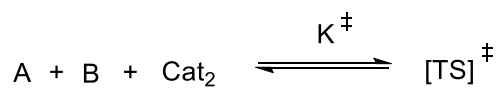
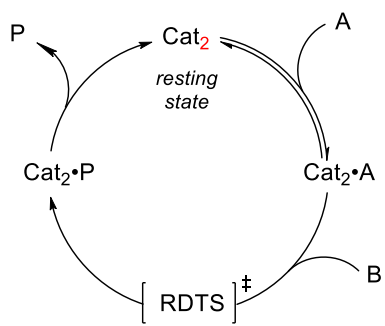
$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [B] * [\text{Cat}]} \quad \text{rate} \propto [A] * [B] * [\text{Cat}]$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [B] * [\text{Cat}]^2} \quad \text{rate} \propto [A] * [B] * [\text{Cat}]^2$$

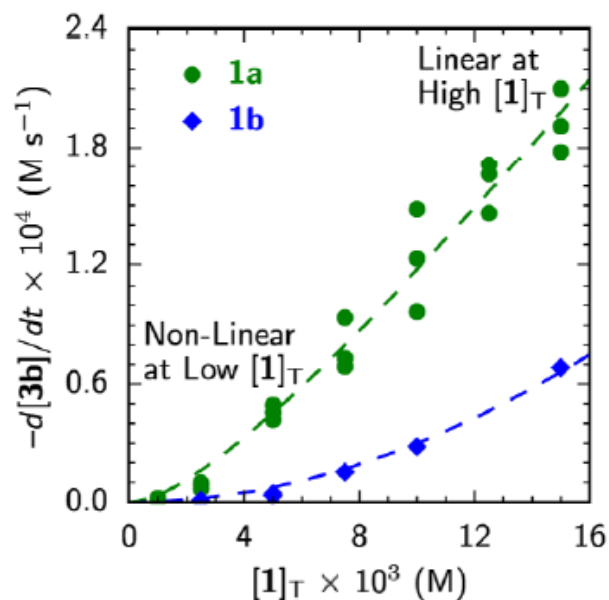
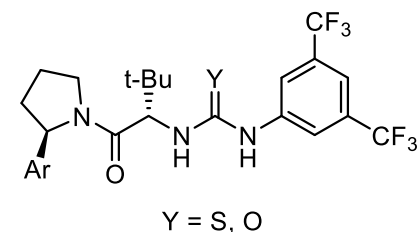
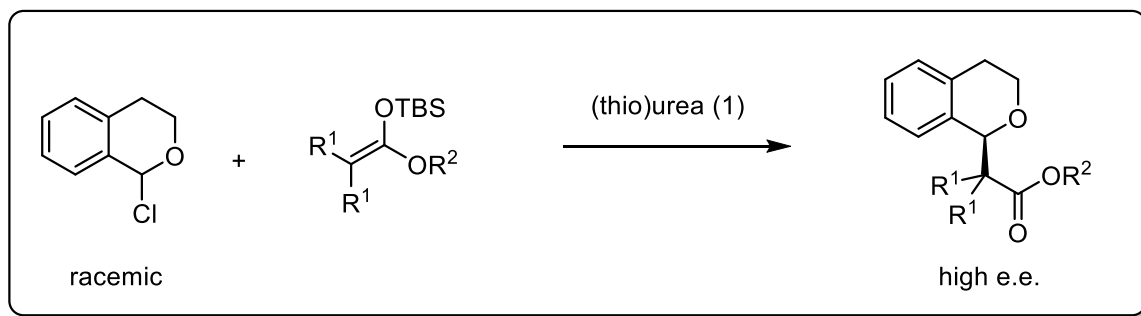
Kinetically indistinguishable!
- both are 1st order in catalyst

Identical RDS –
both involve a catalyst dimer

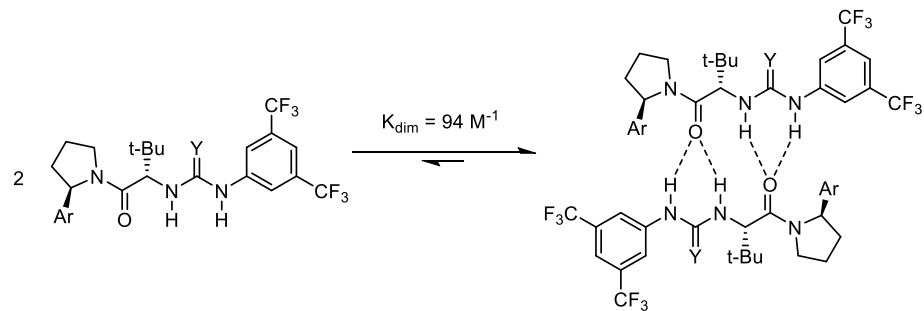


$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [B] * [\text{Cat}_2]} \quad \text{rate} \propto [A] * [B] * [\text{Cat}_2]$$

A catalyst dimer hiding behind a 1st order



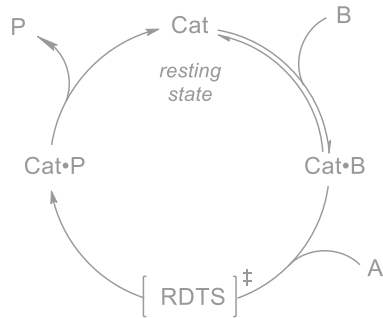
...the resting state of the catalyst is a monomer-dimer equilibrium heavily favoring the dimer:



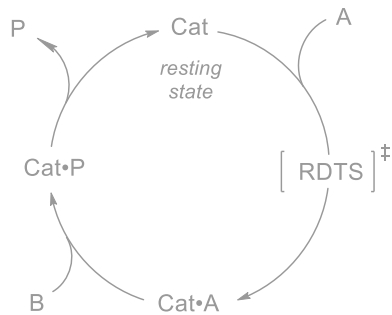
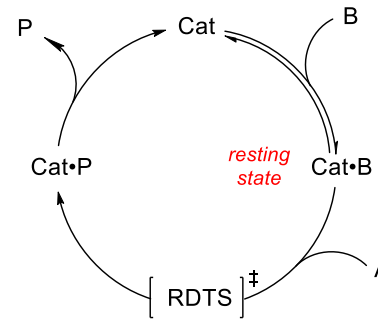
So ~1st order in catalyst =
an RDTs dimer

Approximately linear relationship between $[1]$ and rate:
rxn is roughly 1st order in $[1]$, but...

Saturation kinetics can appear to be a 0th order dependence

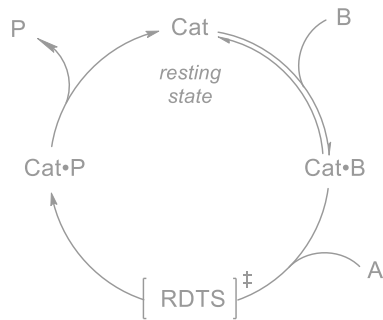


$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [B] * [\text{Cat}]} \quad \text{rate} \propto [A] * [B] * [\text{Cat}]$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [\text{Cat}]} \quad \text{rate} \propto [A] * [\text{Cat}]$$

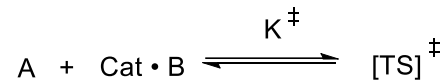
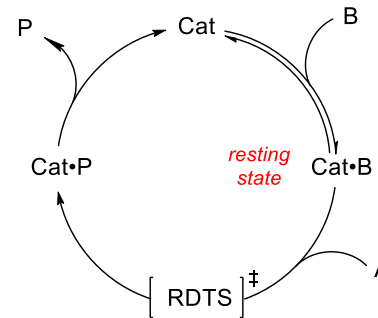
Saturation kinetics can appear to be a 0th order dependence



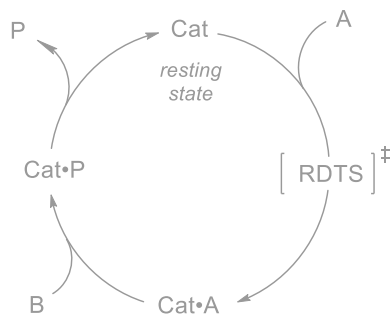
Identical RDTs:
both contain A, B, and cat



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [B] * [\text{Cat}]} \quad \text{rate} \propto [A] * [B] * [\text{Cat}]$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [\text{Cat} \cdot B]} \quad \text{rate} \propto [A] * [\text{Cat} \cdot B]$$



$$K^\ddagger = \frac{[\text{TS}]^\ddagger}{[A] * [\text{Cat}]} \quad \text{rate} \propto [A] * [\text{Cat}]$$

Kinetically indistinguishable!*
both appear 0th order in B

***(technically, the above is saturation kinetics, but it will appear 0th order as long as Cat·B is the dominant resting state)**

Distinguishing between order and molecularity

Molecularity of a species:

- Number of molecules of a reagent that are actually present in a resting state or TS
- Unique to a species/mechanism – it cannot vary with conditions (equilibria can shift to other species)
- Often the thing we are interested in, but only observable indirectly
- Must be an integer for a given species
 - Must be ≥ 0

Kinetic order in a reagent:

- Reflects the difference in molecularity between the resting state(s) and the RDTs(s)
- Can vary with conditions due to changes in the identity of the resting state(s) and the RDTs(s)
- Experimental observable indicating the impact a change in reagent concentration has on reaction rate
 - Can be any number

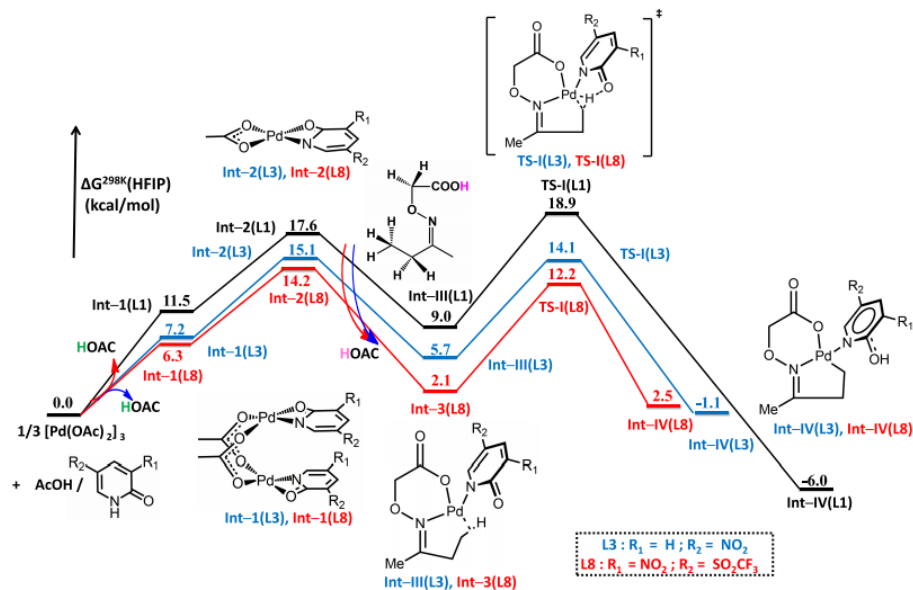
Common mistakes

“It can't be 1.2nd order in catalyst – you can't have 0.2 molecules of catalyst!”

“It's 1st order in catalyst, so it must be monomeric.”

“It's 0th order in that reagent, so it's not involved in the RDTs.”

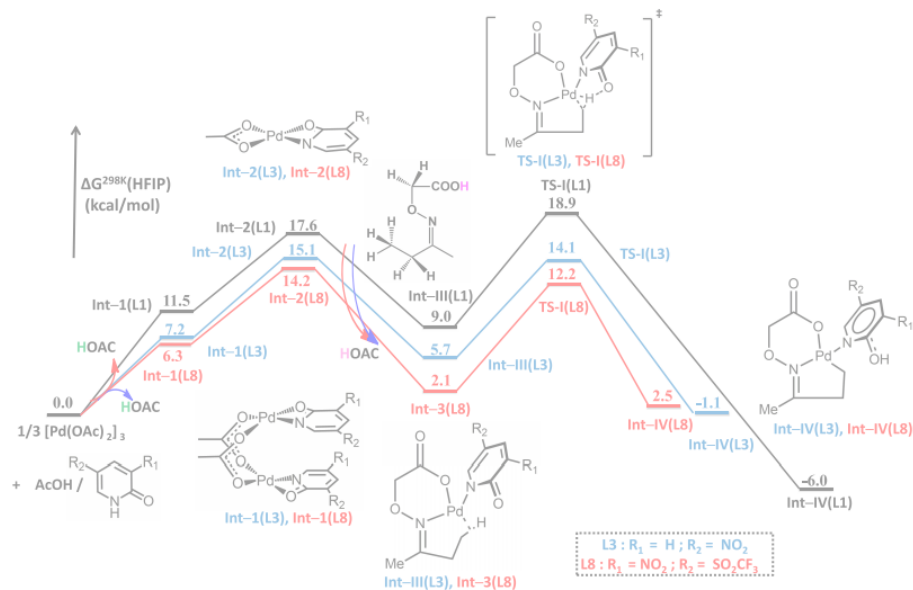
Wait, can't I just compute all of this?



Well, you can compute it...

...but should we trust the computations?

Wait, can't I just compute all of this?



Well, you can compute it...

...but should we trust the computations?

1) Computations are limited by your imagination

2) Computations rely in part on cancellation of errors:

Good at relative energies of similar structures (e.g. diastereomeric TSs)

But potentially problematic when the structures differ significantly (changes in molecularity, charge, solvation, spin state, etc.)

Wait, can't I just compute all of this?

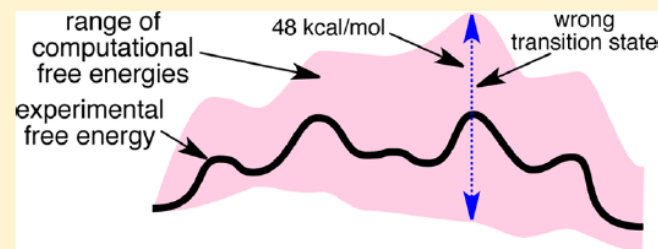
A Case Study of the Mechanism of Alcohol-Mediated Morita Baylis–Hillman Reactions. The Importance of Experimental Observations

R. Erik Plata and Daniel A. Singleton*

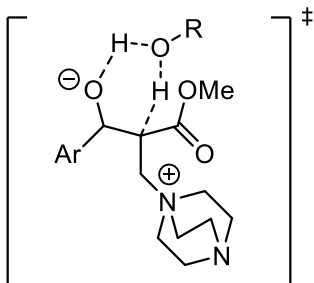
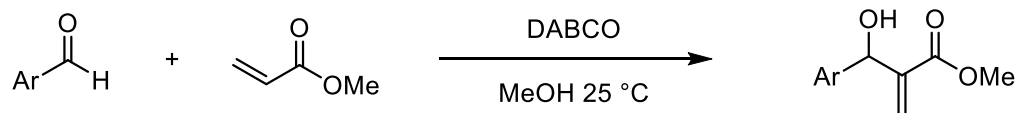
Department of Chemistry, Texas A&M University, College Station, Texas 77842, United States

S Supporting Information

ABSTRACT: The mechanism of the Morita Baylis–Hillman reaction has been heavily studied in the literature, and a long series of computational studies have defined complete theoretical energy profiles in these reactions. We employ here a combination of mechanistic probes, including the observation of intermediates, the independent generation and partitioning of intermediates, thermodynamic and kinetic measurements on the main reaction and side reactions, isotopic incorporation from solvent, and kinetic isotope effects, to define the mechanism and an experimental mechanistic free-energy profile for a prototypical Morita Baylis–Hillman reaction in methanol. The results are then used to critically evaluate the ability of computations to predict the mechanism. The most notable prediction of the many computational studies, that of a proton-shuttle pathway, is refuted in favor of a simple but computationally intractable acid–base mechanism. Computational predictions vary vastly, and it is not clear that any significant accurate information that was not already apparent from experiment could have been garnered from computations. With care, entropy calculations are only a minor contributor to the larger computational error, while literature entropy-correction processes lead to absurd free-energy predictions. The computations aid in interpreting observations but fail utterly as a replacement for experiment.



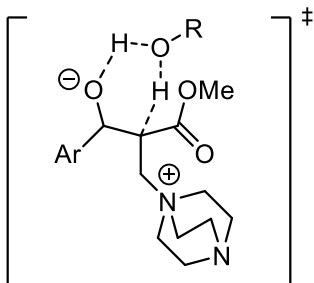
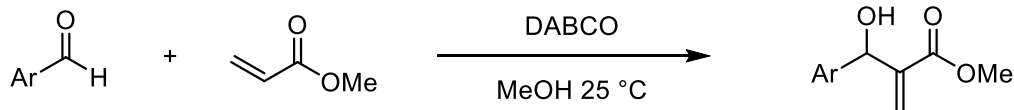
Wait, can't I just compute all of this?



This proton-shuttle mechanism was the "highlight" of most of the computational papers

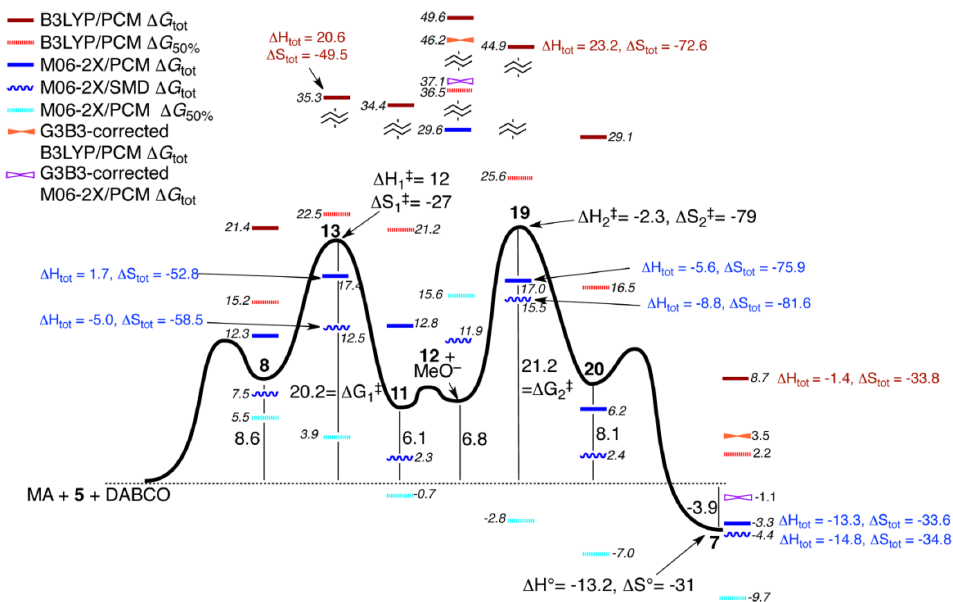
- predicted to be the RDTS by all 7 studies which considered it
- not considered in the other 4 studies
- ruled out by experiment - a simple acid/base mechanism is operative!

Wait, can't I just compute all of this?



This proton-shuttle mechanism was the "highlight" of most of the computational papers

- predicted to be the RDTs by all 7 studies which considered it
- not considered in the other 4 studies
- ruled out by experiment - a simple acid/base mechanism is operative!



“Finally, the errors in relative energetics seen here should be considered in the credence given to the assignment of mechanisms and rate-limiting steps from computational mechanistic studies... Overall, the combination of experimental and computational studies provides a full mechanistic pathway for the MBH reaction including details that would be impossible to discern from either alone.

If absolute rates only tell you about the resting state(s) and the RDTS, then why bother?

1) Determining the kinetic order in a reagent or reagents

- determine the presence/absence/molecularity of a species in the RDTS
 - help to support/refute a proposal for the identity of the RDTS
 - help guide other mechanistic studies (e.g. computations)

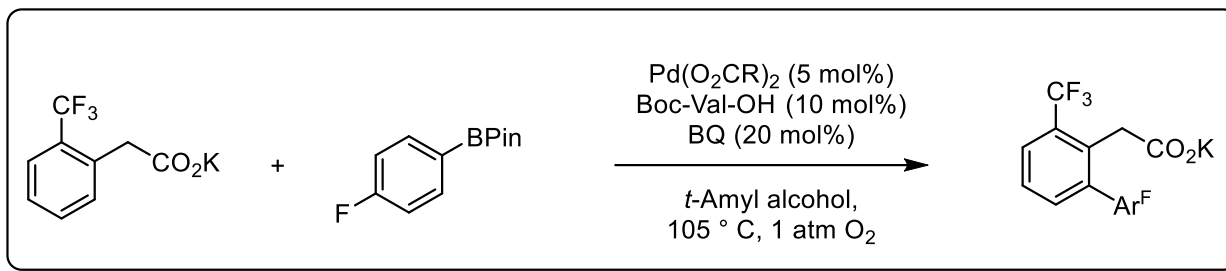
2) Examine how the rate law changes over the reaction

- Identify induction periods
- Identify catalyst deactivation

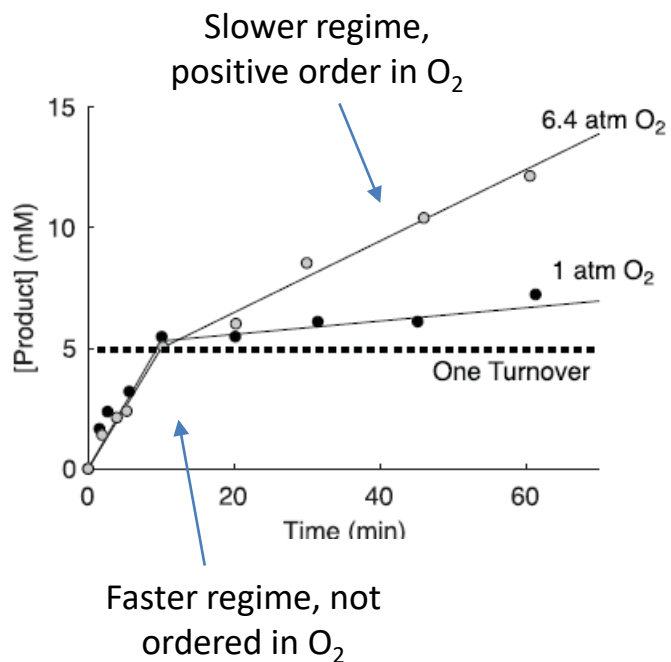
3) Identify changes in bonding or charge between the resting state and RDTS

- Separate-pot KIE experiments
- LFERs (e.g. Hammett plots)

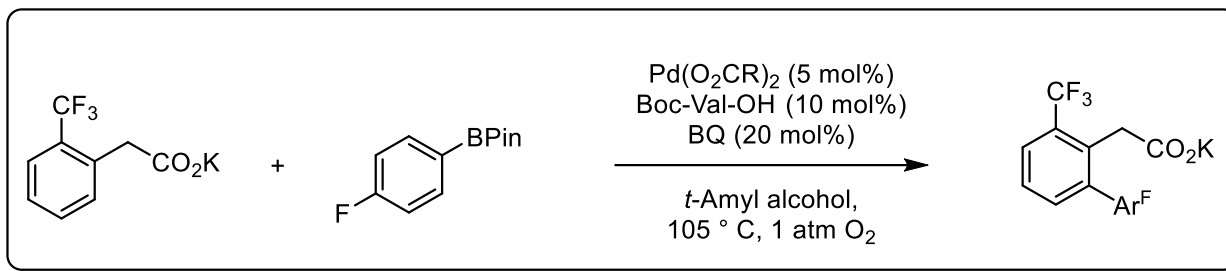
Using time-course data to identify and resolve catalyst inhibition in Pd(II)-(0) cycles



Kinetics suggest Pd reoxidation becomes the RDS

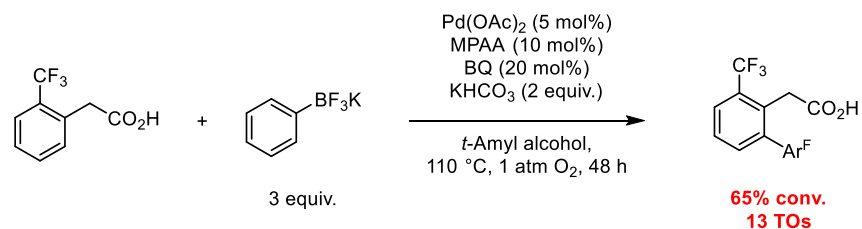
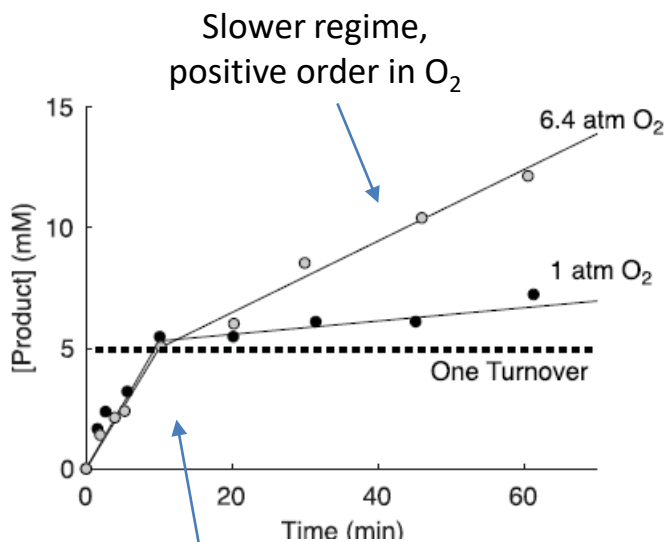


Using time-course data to identify and resolve catalyst inhibition in Pd(II)-(0) cycles

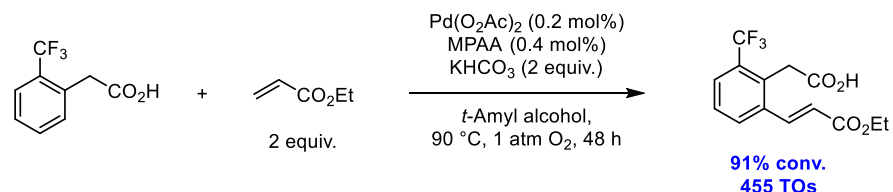


Kinetics suggest Pd reoxidation becomes the RDTS

Based on comparison of arylation and olefination, they hypothesize that BQ is inhibiting reoxidation*

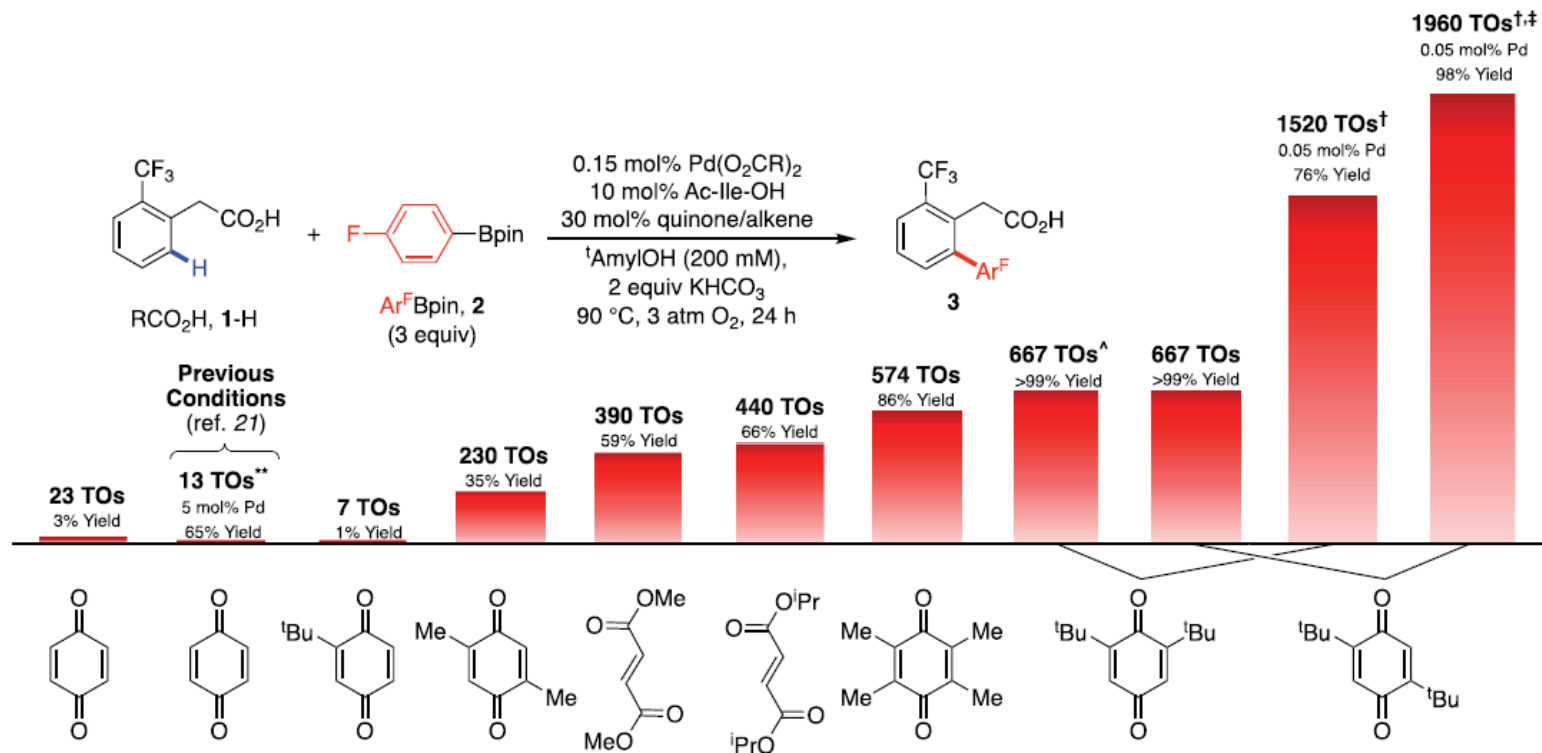


Vs.

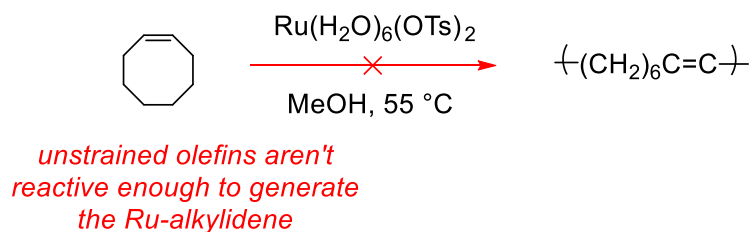
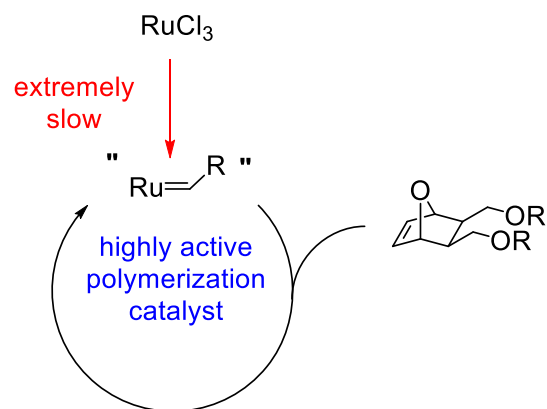
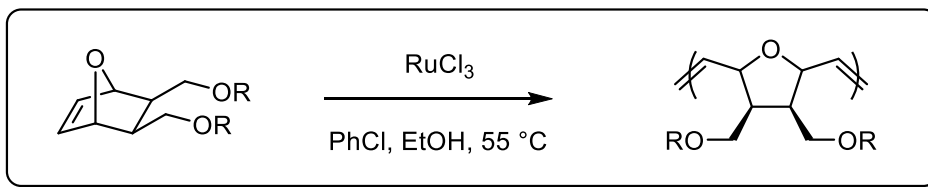


*this is a bit of a logical leap – it would have been nice if they had shown an inverse order in BQ and/or that adding BQ to the olefination caused comparable inhibition

Using time-course data to identify and resolve catalyst inhibition in Pd(II)-(0) cycles

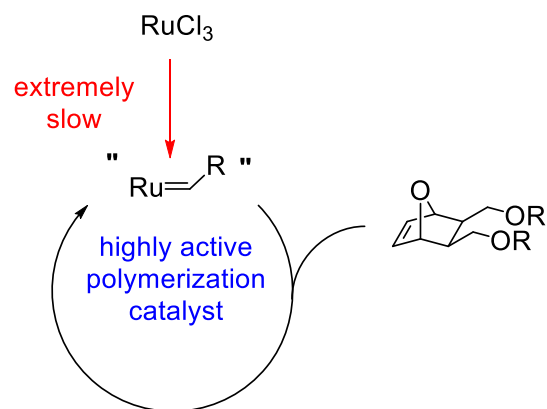
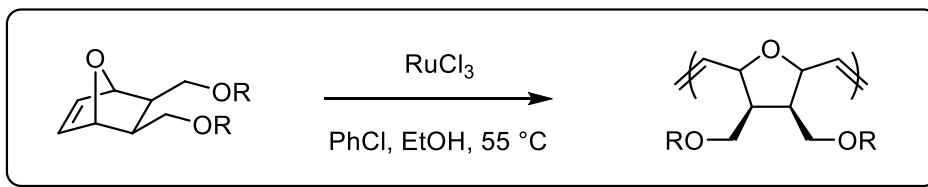


Drawing inspiration for metathesis catalyst design from an induction period

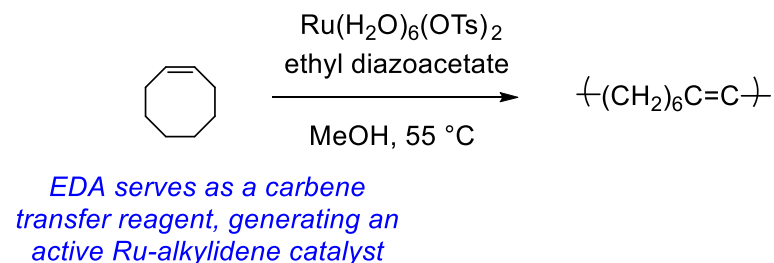
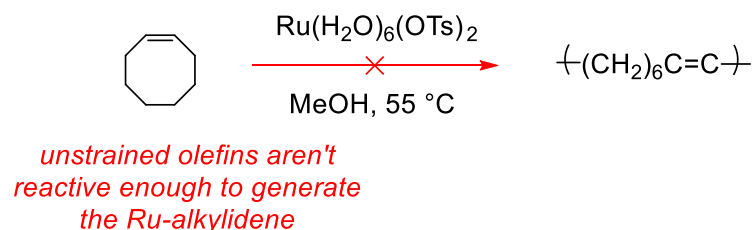


"Polymerization using these group VIII metals are preceded by a sometimes lengthy initiation period [hours to days] that effectively limits their usefulness. It is during this initiation period that a small amount of reactive metal carbene is formed, which then very rapidly polymerizes the cyclic olefin present."

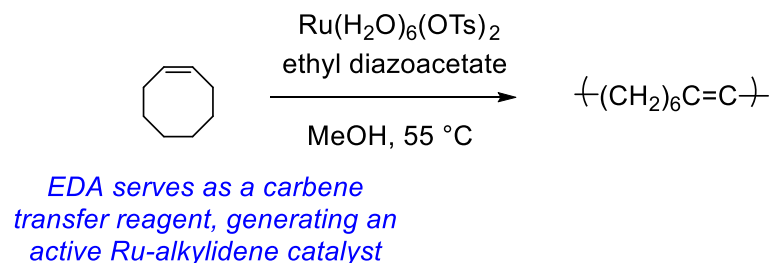
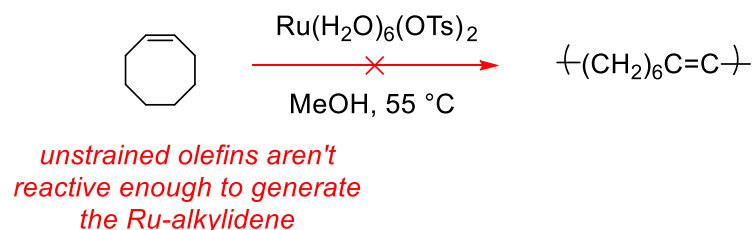
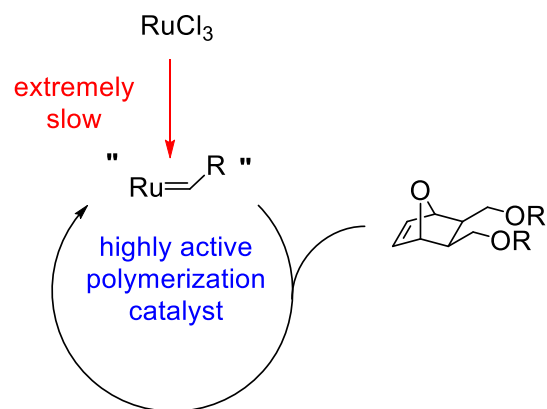
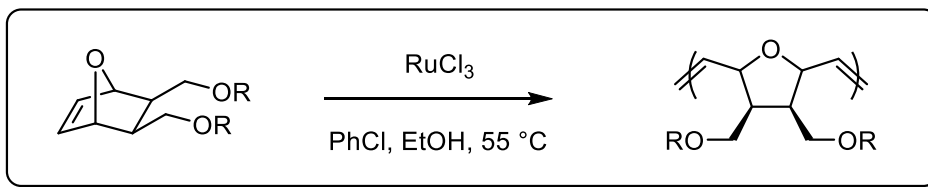
Drawing inspiration for metathesis catalyst design from an induction period



“Polymerization using these group VIII metals are preceded by a sometimes lengthy initiation period [hours to days] that effectively limits their usefulness. It is during this initiation period that a small amount of reactive metal carbene is formed, which then very rapidly polymerizes the cyclic olefin present.”

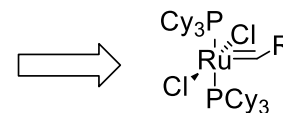


Drawing inspiration for metathesis catalyst design from an induction period



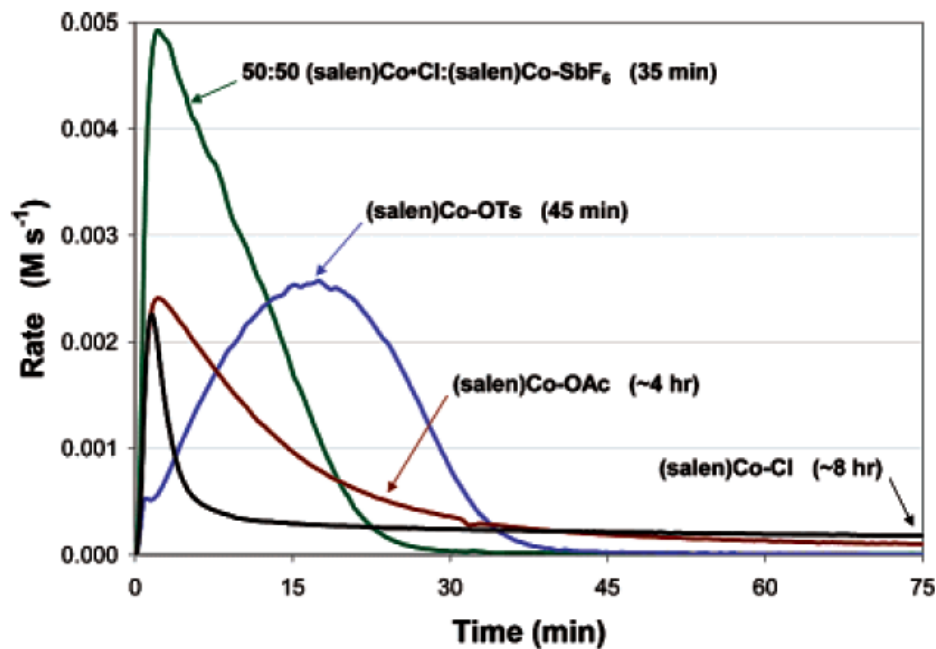
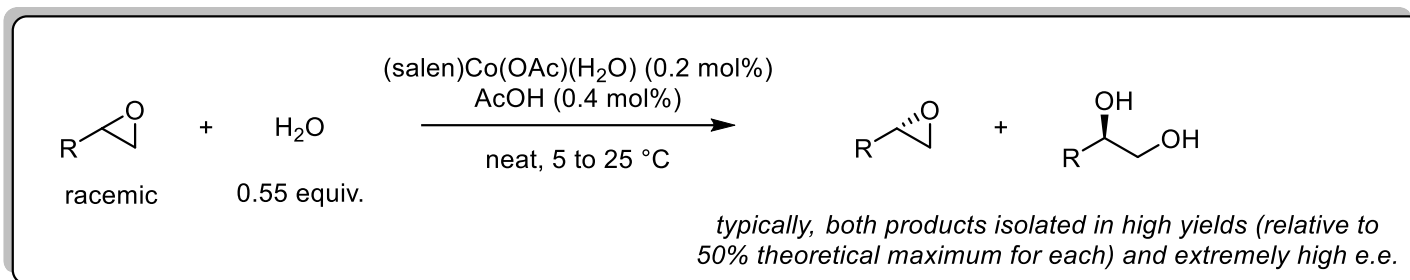
"Polymerization using these group VIII metals are preceded by a sometimes lengthy initiation period [hours to days] that effectively limits their usefulness. It is during this initiation period that a small amount of reactive metal carbene is formed, which then very rapidly polymerizes the cyclic olefin present."

Proof that pre-generated Ru-alkylidenes are highly active for olefin metathesis!



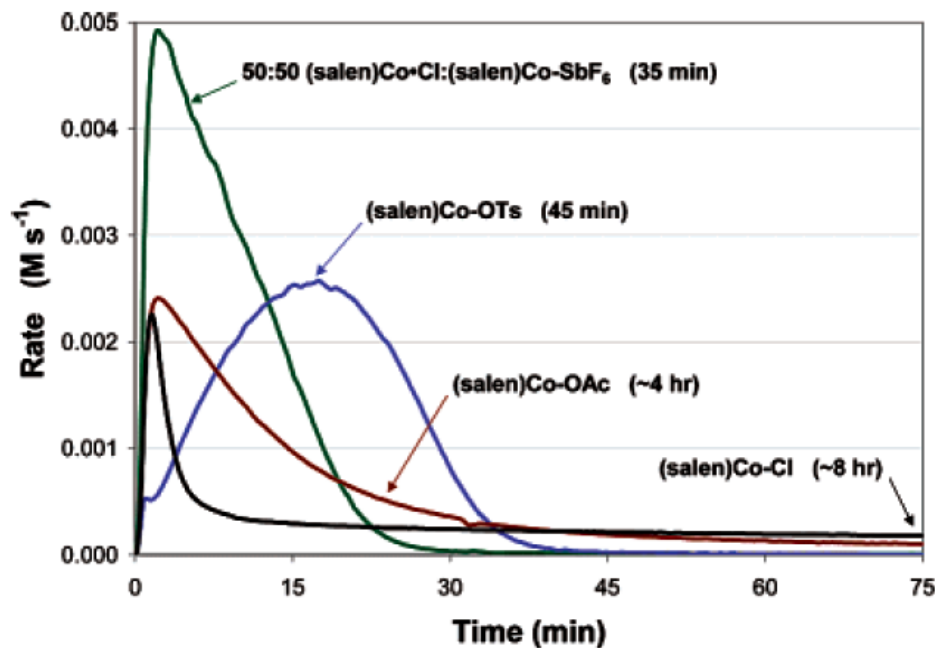
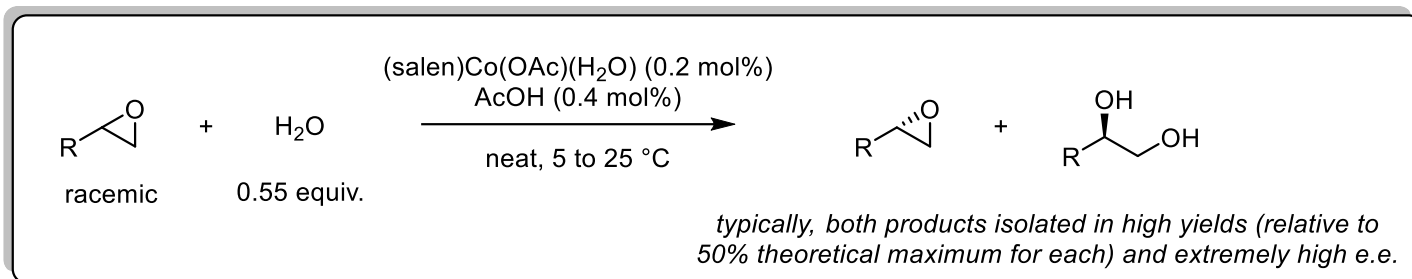
Grubbs 1st-gen

Optimizing rate by balancing complex speciation requirements in the HKR

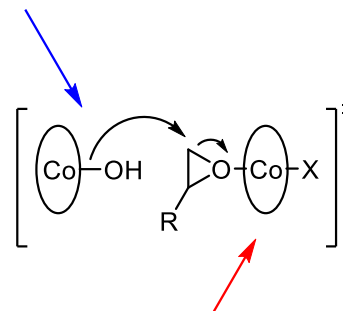


Evidence of an induction period and catalyst deactivation!

Optimizing rate by balancing complex speciation requirements in the HKR



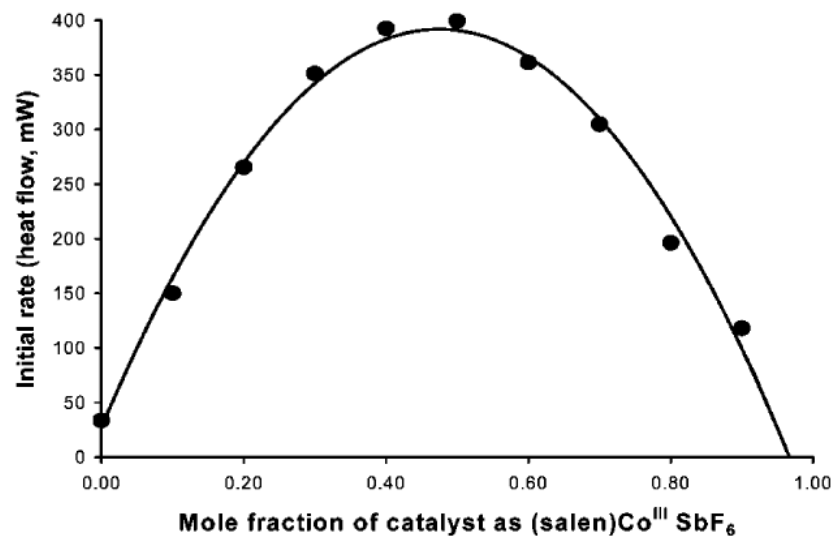
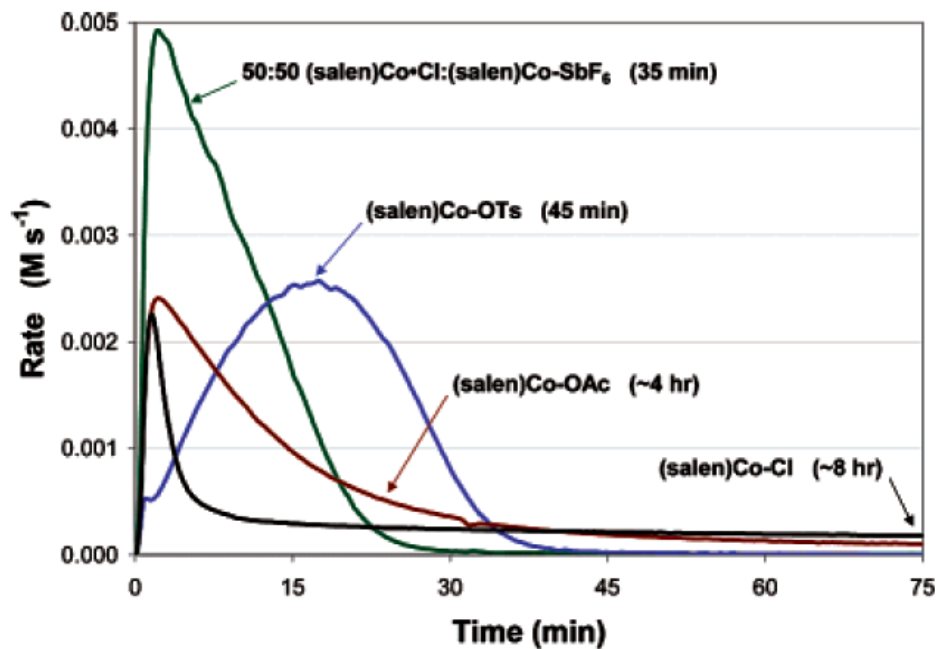
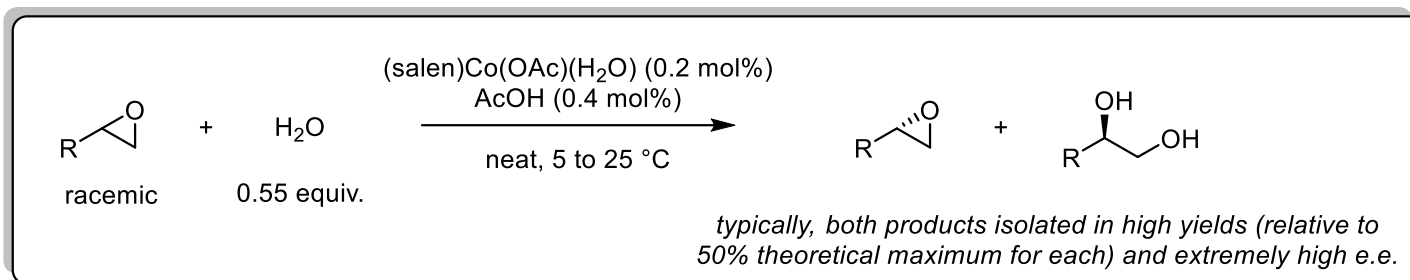
This has to be Co-OH, but at the start of the reaction, [Co-OH] = 0
 → induction period as Co-X converts to Co-OH



This Co is a Lewis acid: Co-OH will be less reactive than Co-OAc
 → deactivation as Co-X converts to Co-OH

Evidence of an induction period and catalyst deactivation!

Optimizing rate by balancing complex speciation requirements in the HKR



Evidence of an induction period and catalyst deactivation!

If absolute rates only tell you about the resting state(s) and the RDTS, then why bother?

1) Determining the kinetic order in a reagent or reagents

- determine the presence/absence/molecularity of a species in the RDTS
 - help to support/refute a proposal for the identity of the RDTS
 - help guide other mechanistic studies (e.g. computations)

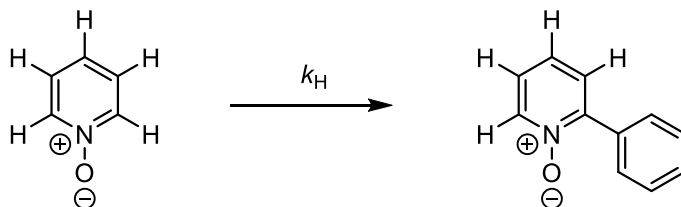
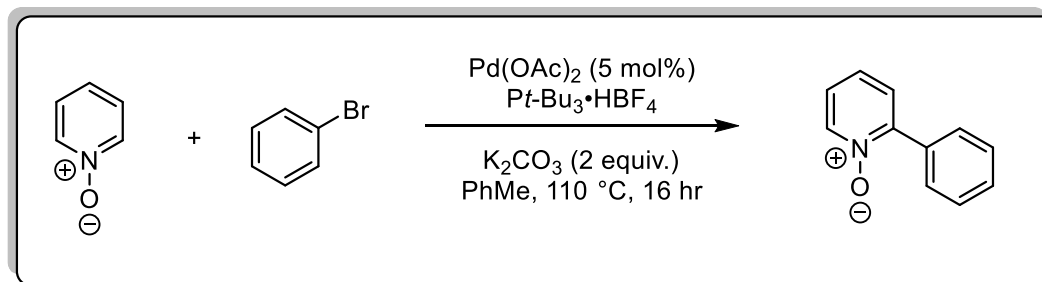
2) Examine how the rate law changes over the reaction

- Identify induction periods
- Identify catalyst deactivation

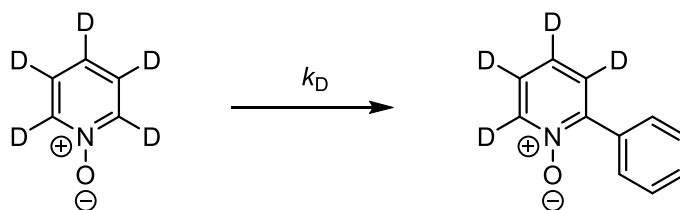
3) Identify changes in bonding or charge between the resting state and RDTS

- Separate-pot KIE experiments
- LFERs (e.g. Hammett plots)

Using an absolute rate KIE experiment to prove rate-determining C-H activation



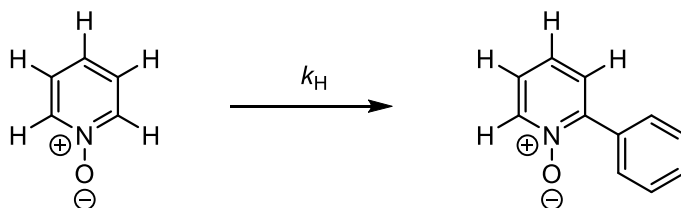
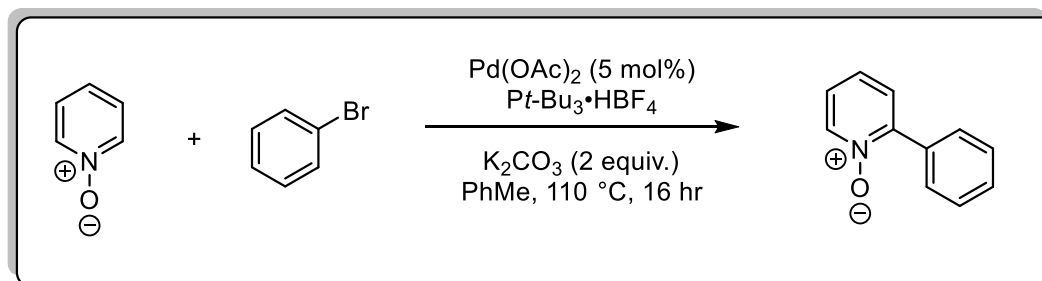
absolute rates = separate pots



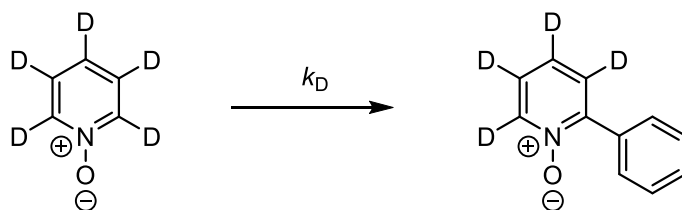
absolute rate $k_{\text{H}}/k_{\text{D}} = 3.3$

C-H cleavage is the RDTS!

Using an absolute rate KIE experiment to prove rate-determining C-H activation



absolute rates = separate pots

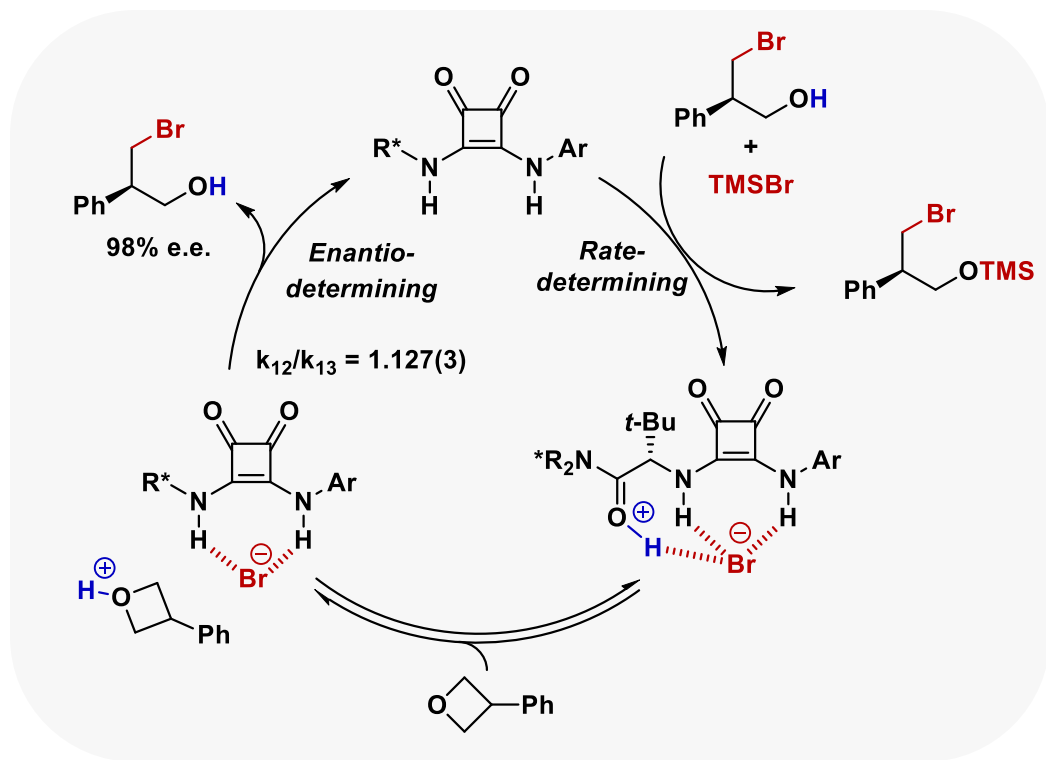


absolute rate $k_H/k_D = 3.3$

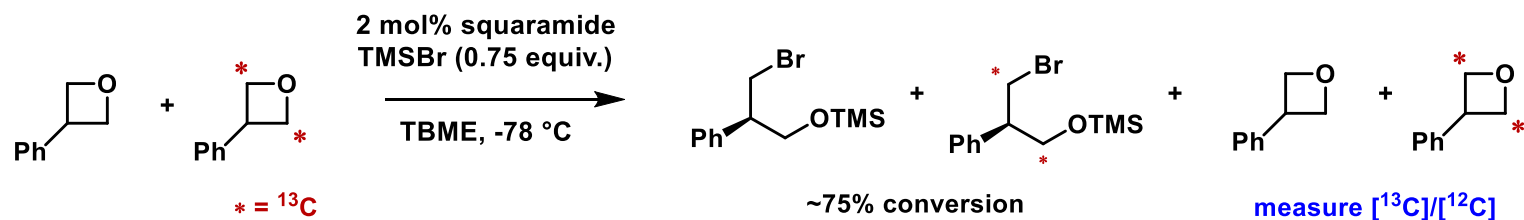
C-H cleavage is the RDTS!

We can say this conclusively because absolute rate experiments only show us the resting state(s) and the RDTS(s) – if we used a competition experiment (relative rate measurement) we could only conclude that the C-H activation is irreversible, not necessarily rate-determining

Proposed catalytic cycle at steady-state for HBr co-catalyzed oxetane opening

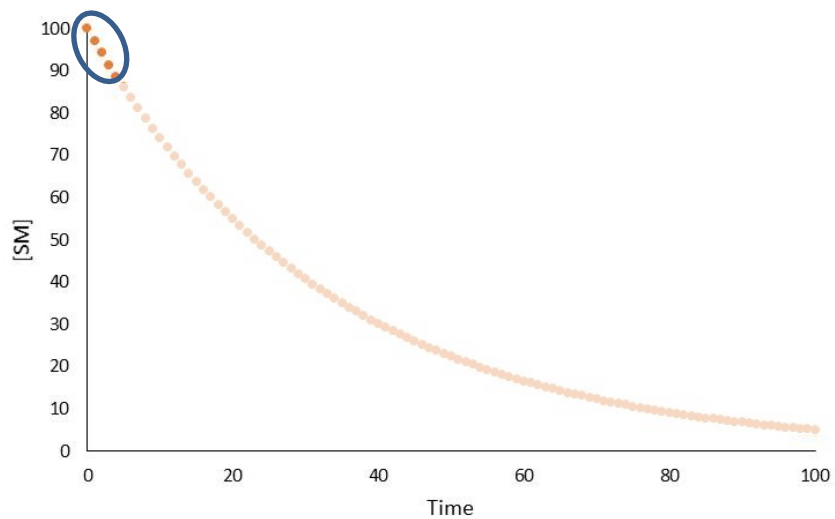


- Order in proton source, 1st order in catalyst, saturation in TMSBr, 0th order in oxetane
- Buildup of free catalyst and bromohydrin at steady state
- Observable catalyst-HBr complex
- Primary KIE in a one-pot competition experiment indicates reversible oxetane activation, enantiodetermining bromide delivery



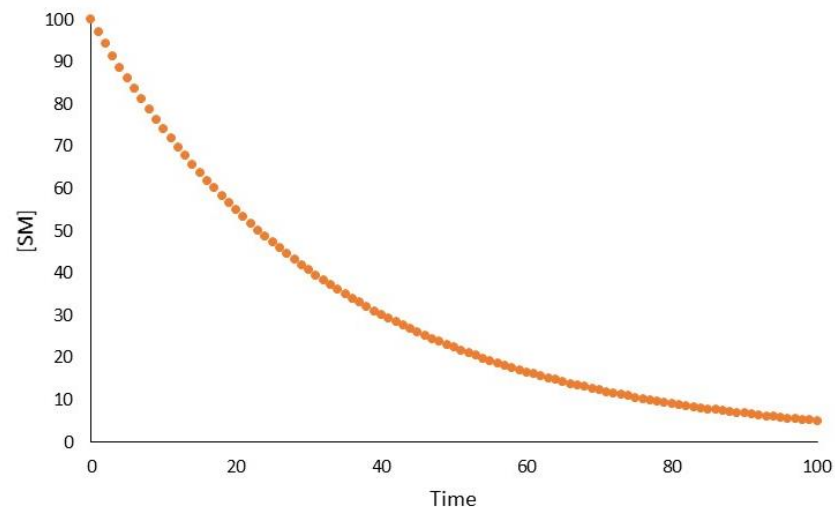
A brief introduction to measuring absolute rates

Initial rate kinetics



vs.

Reaction time course monitoring



These are complimentary tools!

Determining absolute rates – how not to do it*

*unless you already know the reactions are kinetically well behaved, have identical rate laws, and you know the overall order

Reaction	% conv at a given time
Rxn A	50%
Rxn B	75%

Can we say how much faster Rxn B is than Rxn A based on these data?

Determining absolute rates – how not to do it*

*unless you already know the reactions are kinetically well behaved, have identical rate laws, and you know the overall order

Reaction	% conv at a given time
Rxn A	50%
Rxn B	75%

Can we say how much faster Rxn B is than Rxn A based on these data?

No! Rxn A could even be faster!

Determining absolute rates – how not to do it*

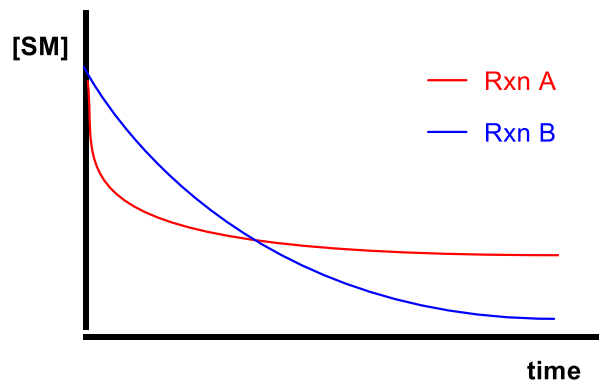
*unless you already know the reactions are kinetically well behaved, have identical rate laws, and you know the overall order

Reaction	% conv at a given time
Rxn A	50%
Rxn B	75%

Can we say how much faster Rxn B is than Rxn A based on these data?

No! Rxn A could even be faster!

1) Rxn A could be faster but stall at lower conversion[^] (or Rxn A could have a longer induction period than Rxn B)



[^]This is more common than you might think – the same structural changes that make a catalyst more reactive (e.g. open coordination sites) can make it more prone to decomposition

Determining absolute rates – how not to do it*

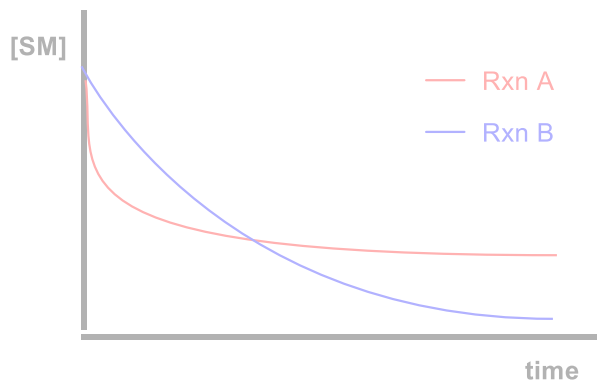
*unless you already know the reactions are kinetically well behaved, have identical rate laws, and you know the overall order

Reaction	% conv at a given time
Rxn A	50%
Rxn B	75%

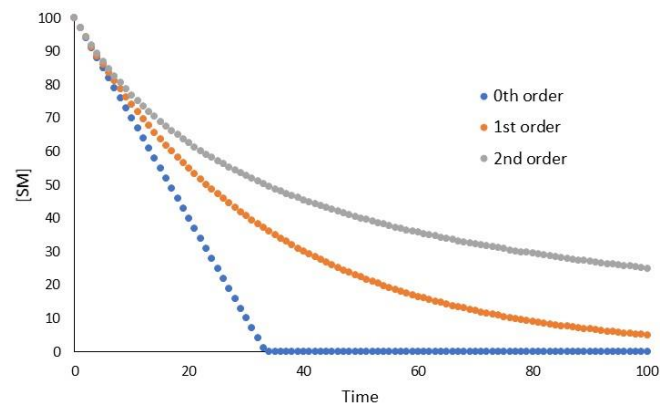
Can we say how much faster Rxn B is than Rxn A based on these data?

No! Rxn A could even be faster!

1) Rxn A could be faster but stall at lower conversion[^] (or Rxn A could have a longer induction period than Rxn B)



2) Even for kinetically well-behaved reactions, you can't compute rate from a single time point without knowing the overall order



[^]This is more common than you might think – the same structural changes that make a catalyst more reactive (e.g. open coordination sites) can make it more prone to decomposition

Determining absolute rates – how not to do it*

*unless you already know the reactions are kinetically well behaved, have identical rate laws, and you know the overall order

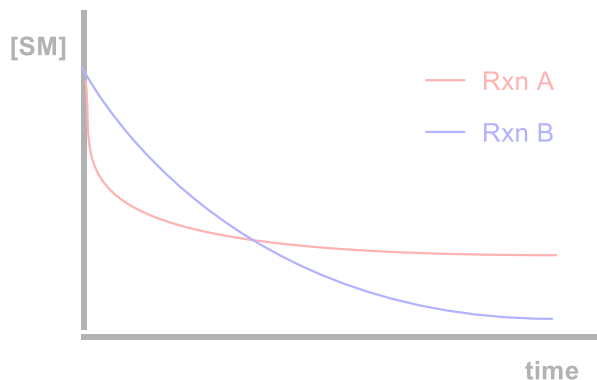
Reaction	% conv at a given time
Rxn A	50%
Rxn B	75%

Can we say how much faster Rxn B is than Rxn A based on these data?

No! Rxn A could even be faster!

1) Rxn A could be faster but stall at lower conversion[^] (or Rxn A could have a longer induction period than Rxn B)

2) Even for kinetically well-behaved reactions, you can't compute rate from a single time point without knowing the overall order



Order	k_B/k_A
0 th	1.5
1 st	2
2 nd	3

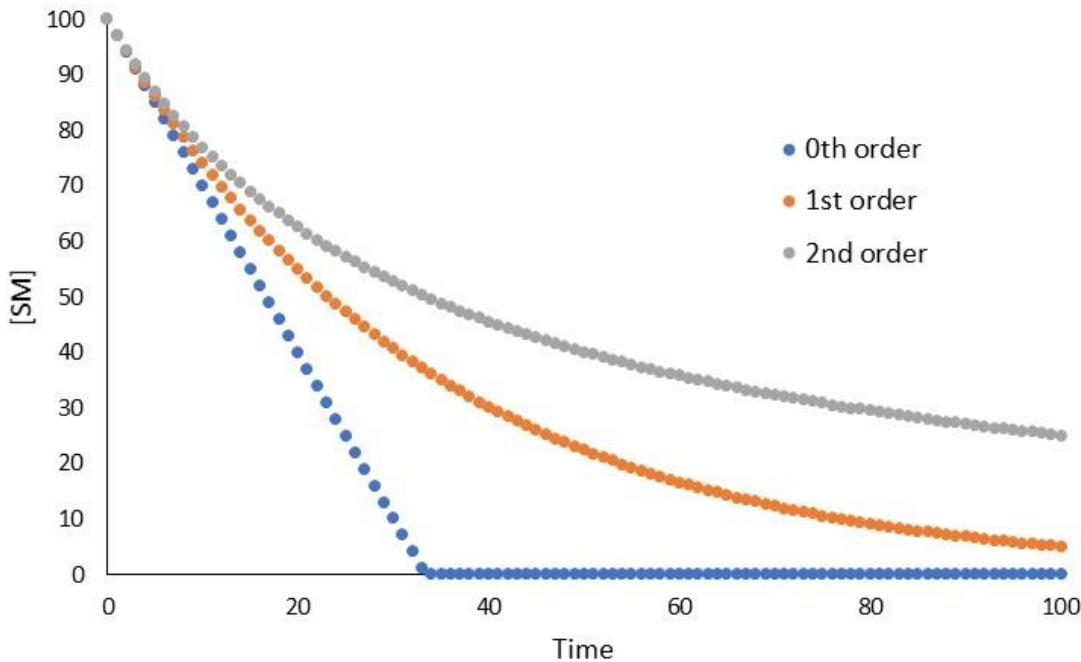
[^]This is more common than you might think – the same structural changes that make a catalyst more reactive (e.g. open coordination sites) can make it more prone to decomposition

Determining absolute rates

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative



For a non-0th order reaction, rate depends on the concentration of one or more reagent

rate will vary over the course of the reaction and a plot of [reagent] vs. time will exhibit curvature

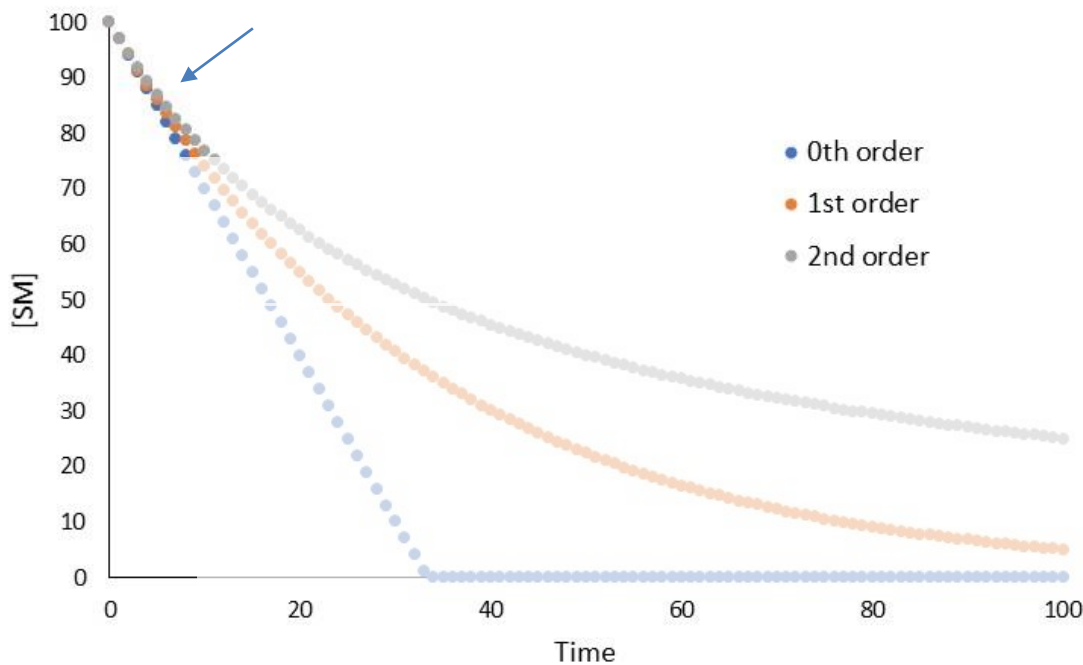
Determining absolute rates – initial rates kinetics

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative

All exhibit nearly linear behavior at low conversion



For a non-0th order reaction, rate depends on the concentration of one or more reagent

rate will vary over the course of the reaction and a plot of [reagent] vs. time will exhibit curvature

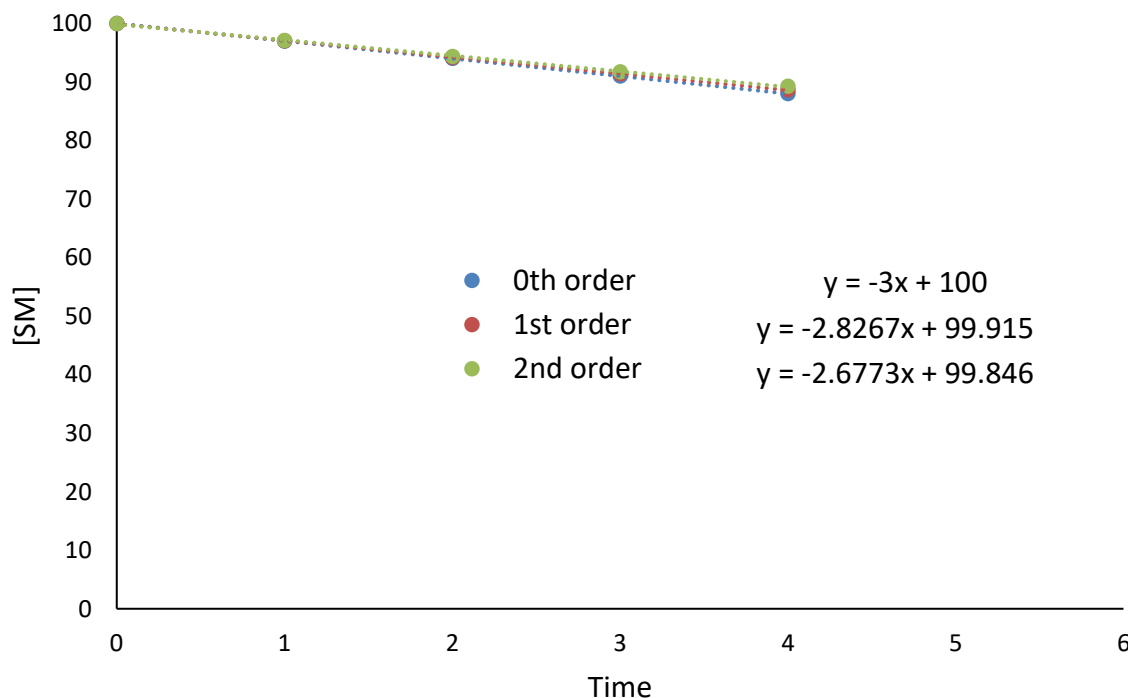
but over a small conversion window, the changes in concentrations (and thus, rate) will be minimal -> we can approximate the derivative with a linear fit

Determining absolute rates – initial rates kinetics

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative



For a non-0th order reaction, rate depends on the concentration of one or more reagent

rate will vary over the course of the reaction and a plot of [reagent] vs. time will exhibit curvature

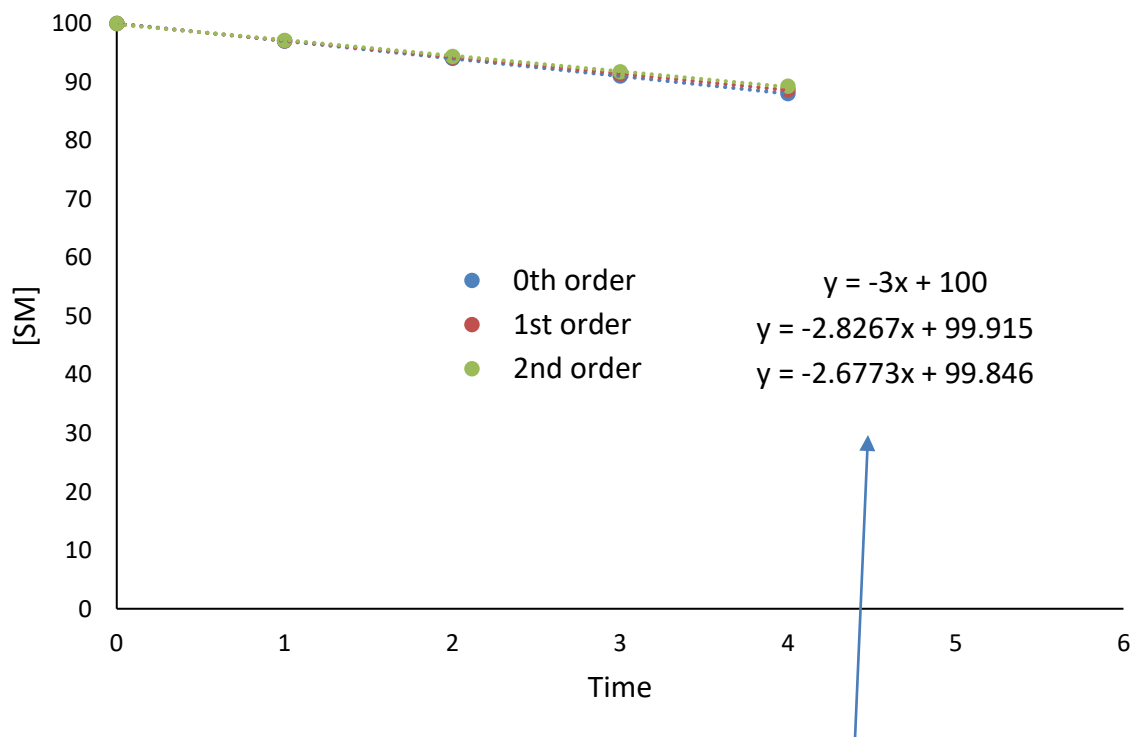
but over a small conversion window, the changes in concentrations (and thus, rate) will be minimal -> we can approximate the derivative with a linear fit

Determining absolute rates – initial rates kinetics

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative



For a non-0th order reaction, rate depends on the concentration of one or more reagent

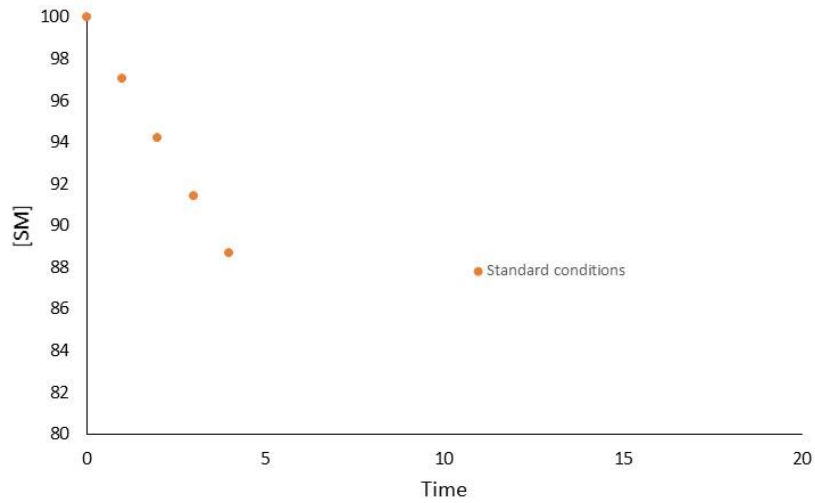
rate will vary over the course of the reaction and a plot of [reagent] vs. time will exhibit curvature

but over a small conversion window, the changes in concentrations (and thus, rate) will be minimal -> we can approximate the derivative with a linear fit

Fitting error is ~10%, which is probably pretty similar to the experimental error you will have

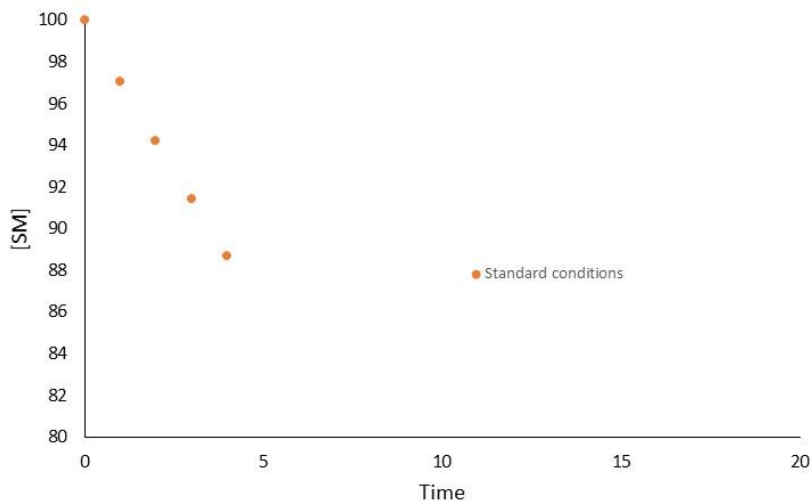
Determining absolute rates – initial rates kinetics

- 1) Collect [] vs. time data over a window of ~10% conversion*
-> try to have at least 5 data points spread out between 0 and ~10% conversion*



Determining absolute rates – initial rates kinetics

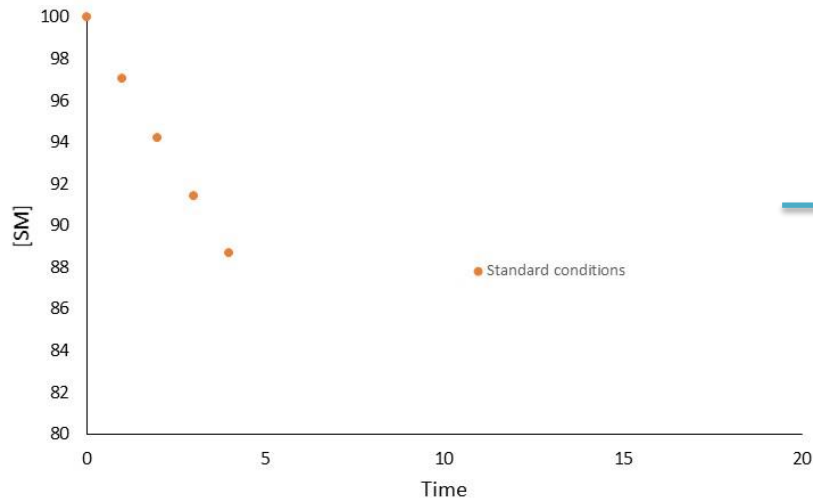
- 1) Collect [] vs. time data over a window of ~10% conversion*
-> try to have at least 5 data points spread out between 0 and ~10% conversion*



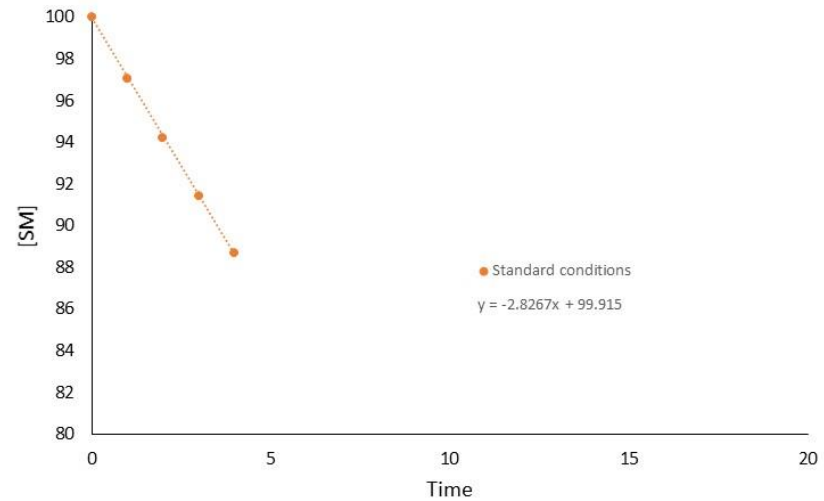
*really, what you need is a regime where the [] of all ordered reagents changes little enough that [] vs. time is roughly linear – 0-10% will generally be safe for a reaction that reaches complete conversion, but if your reaction stalls out at low conversion (catalyst death is rapid or an extremely potent inhibitor is generated) you will need to use a smaller window. A safe bet is looking at 0-10% **of the conversion your reaction can reach**

Determining absolute rates – initial rates kinetics

- 1) Collect [] vs. time data over a window of $\sim 10\%$ conversion*
-> try to have at least 5 data points spread out between 0 and $\sim 10\%$ conversion*

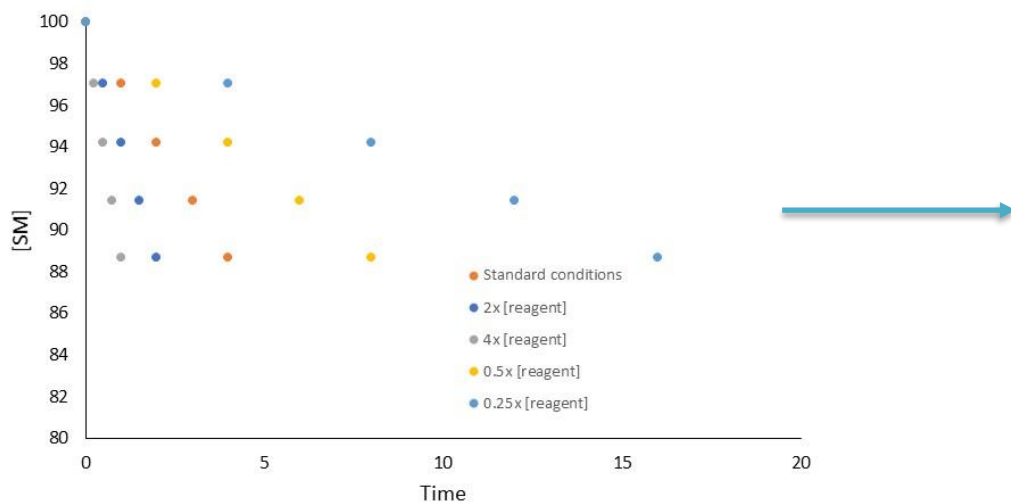


- 2) Fit the data to a line – the slope of the line is k_{obs} under those reaction conditions

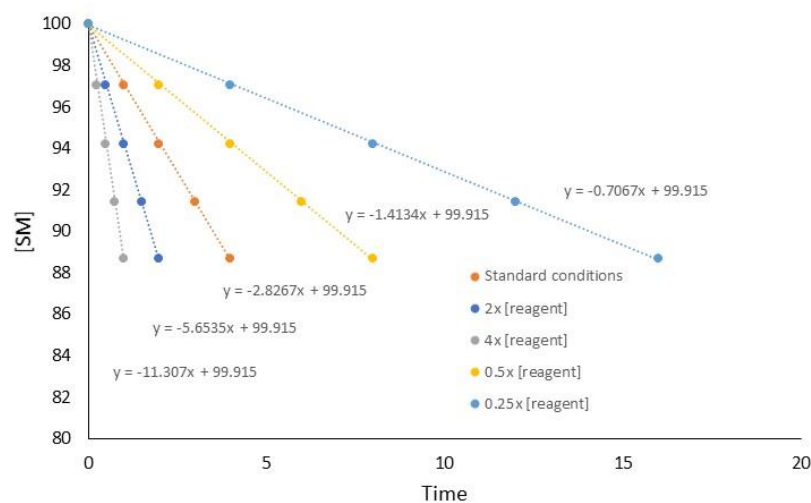


Determining absolute rates – initial rates kinetics

- 1) Collect [] vs. time data over a window of $\sim 10\%$ conversion*
-> try to have at least 5 data points spread out between 0 and $\sim 10\%$ conversion*



- 2) Fit the data to a line – the slope of the line is k_{obs} under those reaction conditions

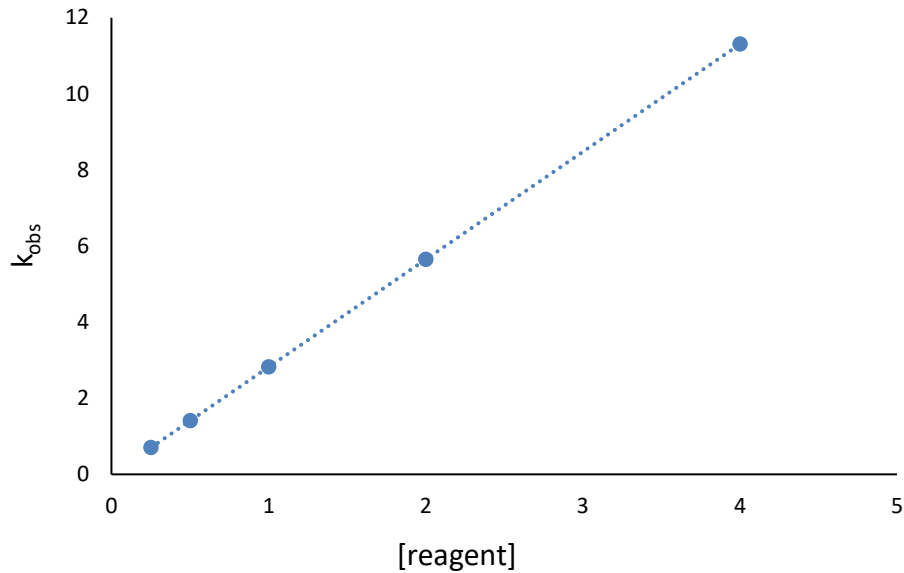


- 3) Repeat steps 1 and 2 varying the starting concentration of the reagent of interest
-> try to have at least 5 data. Ideally, they should span a concentration range of ~ 1 order of magnitude centered on your standard reaction conditions

Determining absolute rates – initial rates kinetics

4) Plot k_{obs} vs. [reagent] to determine order.

NB – when fitting the data do not force the fit through the origin



In this case, k_{obs} varies linearly with [reagent] -
> the reaction is 1st order in that reagent

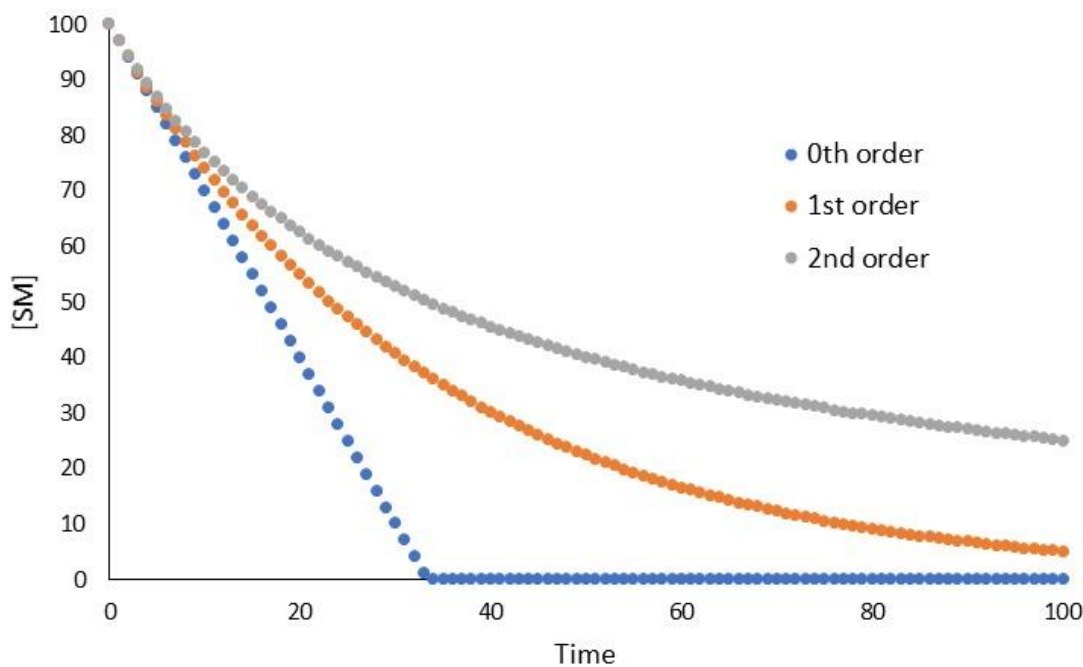
5) Repeat the whole process as necessary for other reagents of interest

Determining absolute rates – using the full reaction time-course

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative



For a non-0th order reaction, rate depends on the concentration of one or more reagent

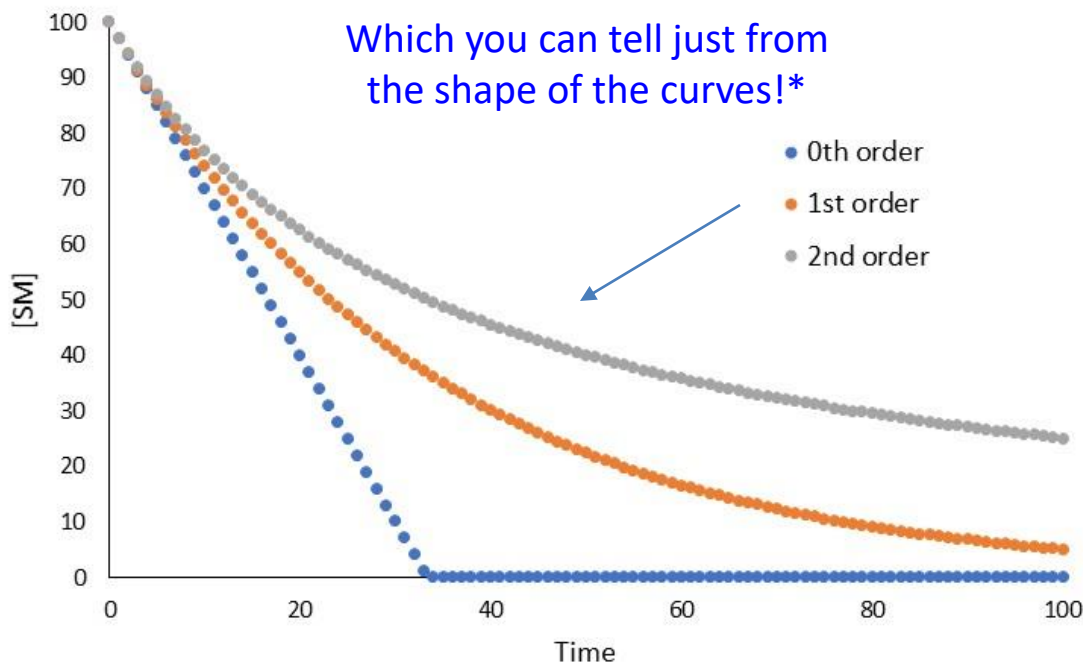
rate will vary over the course of the reaction and a plot of [reagent] vs. time will exhibit curvature

Determining absolute rates – using the full reaction time-course

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative



For a non-0th order reaction, rate depends on the concentration of one or more reagent

rate will vary over the course of the reaction and a plot of [reagent] vs. time will exhibit curvature

we can use that curvature to determine the relationship between reagent concentration and rate

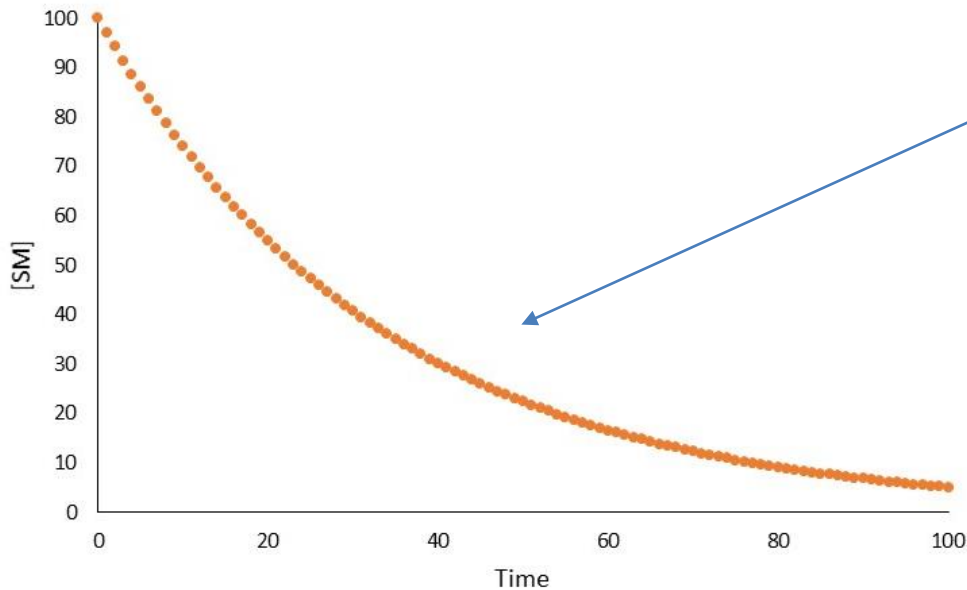
*don't actually try to do this just by eye, instead use graphical fitting methods from Blackmond and Bures

Determining absolute rates – using the full reaction time-course

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative



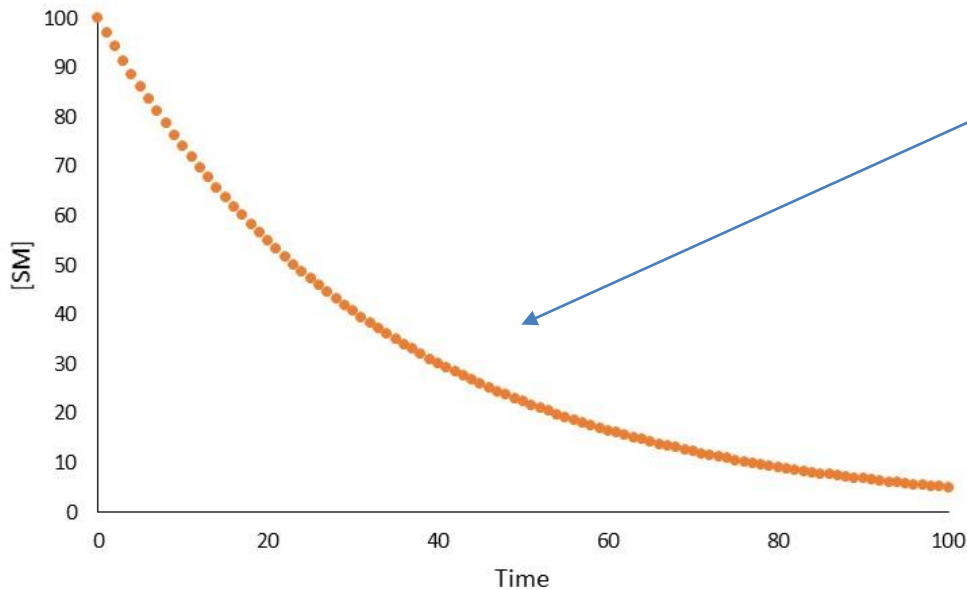
How do we find an expression for the derivative of this curve?

Determining absolute rates – using the full reaction time-course

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative



How do we find an expression for the derivative of this curve?

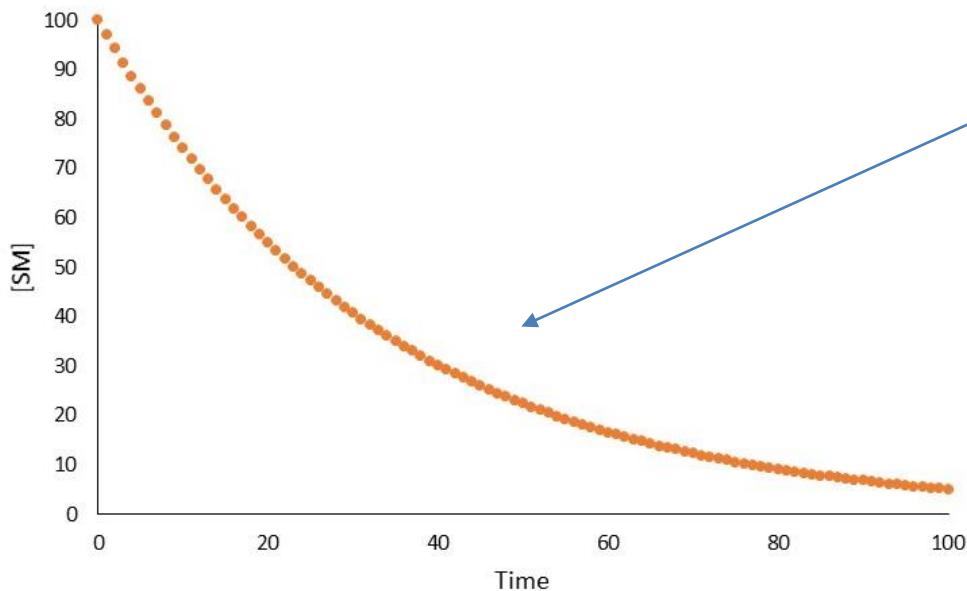
-> Old-school approach – use flooding kinetics (pseudo-1st order conditions) to help simplify the data and attempt to fit to known expressions for integrated rate laws of various orders

Determining absolute rates – using the full reaction time-course

Usually, our experimental data will be concentration vs. time



to get rate data, we need to find the derivative



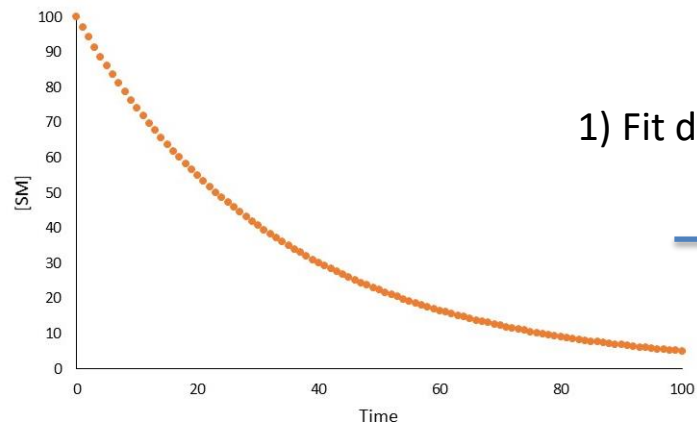
How do we find an expression for the derivative of this curve?

-> Old-school approach – use flooding kinetics (pseudo-1st order conditions) to help simplify the data and attempt to fit to known expressions for integrated rate laws of various orders

-> Modern approach – use a computer to fit the data as is (no need to simplify with pseudo-1st order conditions) – RPKA (differential method) and VTNA (integral method)

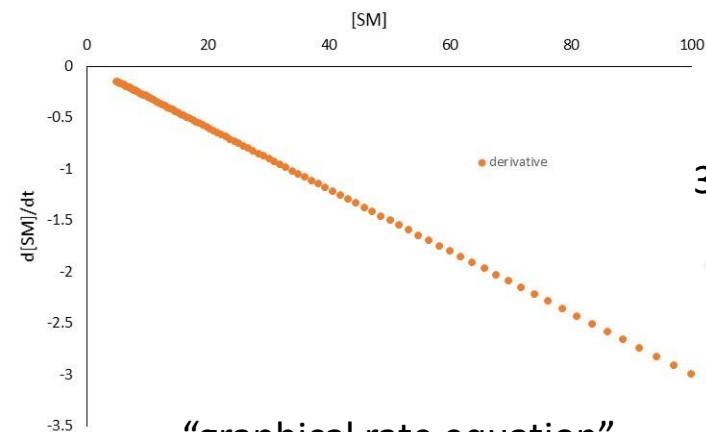
Determining absolute rates – using the full reaction time-course

1) Fit data to a high-order polynomial:



$$[SM] = -1.04 * 10^{-13} * t^7 + 6.06 * 10^{-11} * t^6 - 1.72 * 10^{-8} * t^5 + 3.24 * 10^{-6} * t^4 - 4.5 * 10^{-4} * t^3 + 0.0450 * t^2 - 3.00 * t + 100$$

2) Take the derivative of the polynomial to get an expression for rate as a function of time

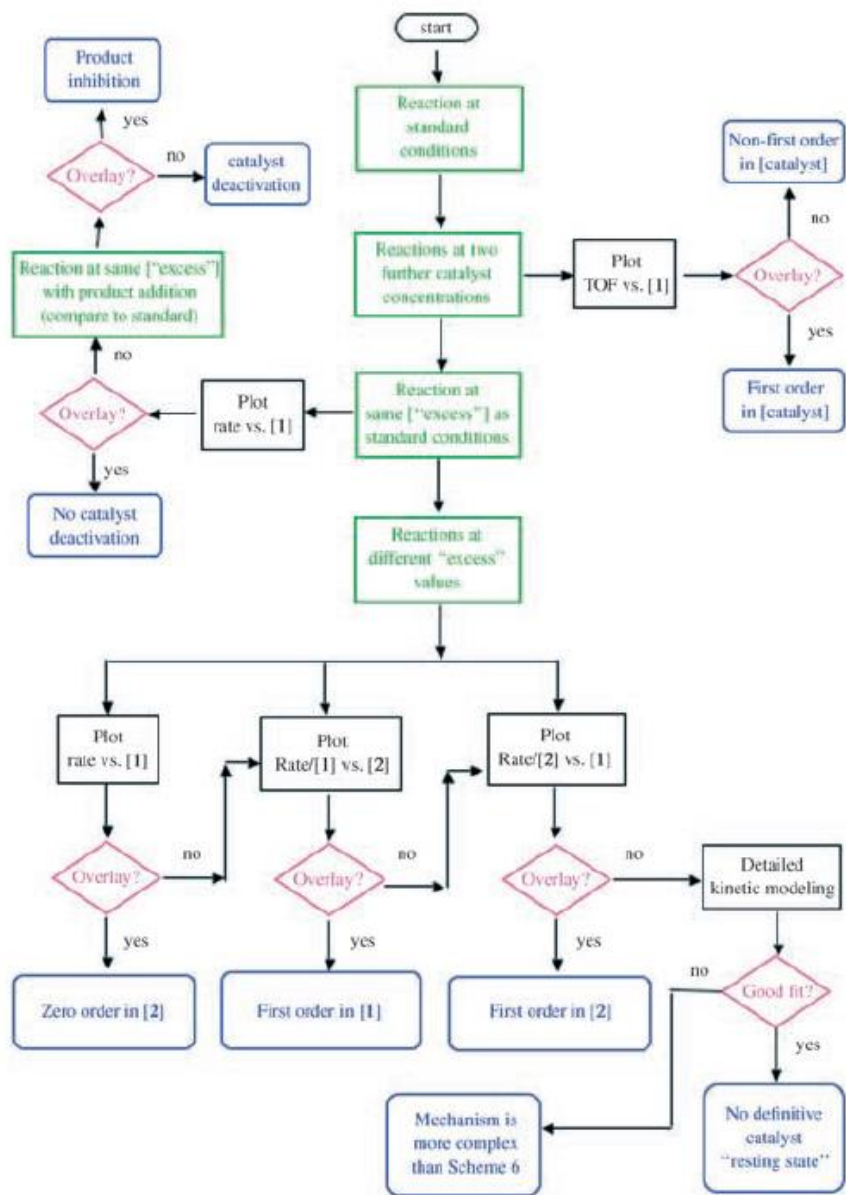


3) Plot rate vs. [reagent]ⁿ

$$\frac{d[SM]}{dt} = -7.25 * 10^{-13} * t^6 + 3.52 * 10^{-10} * t^5 - 8.63 * 10^{-8} * t^4 + 1.30 * 10^{-5} * t^3 - 1.34 * 10^{-3} * t^2 + 0.0899 * t - 3.00$$

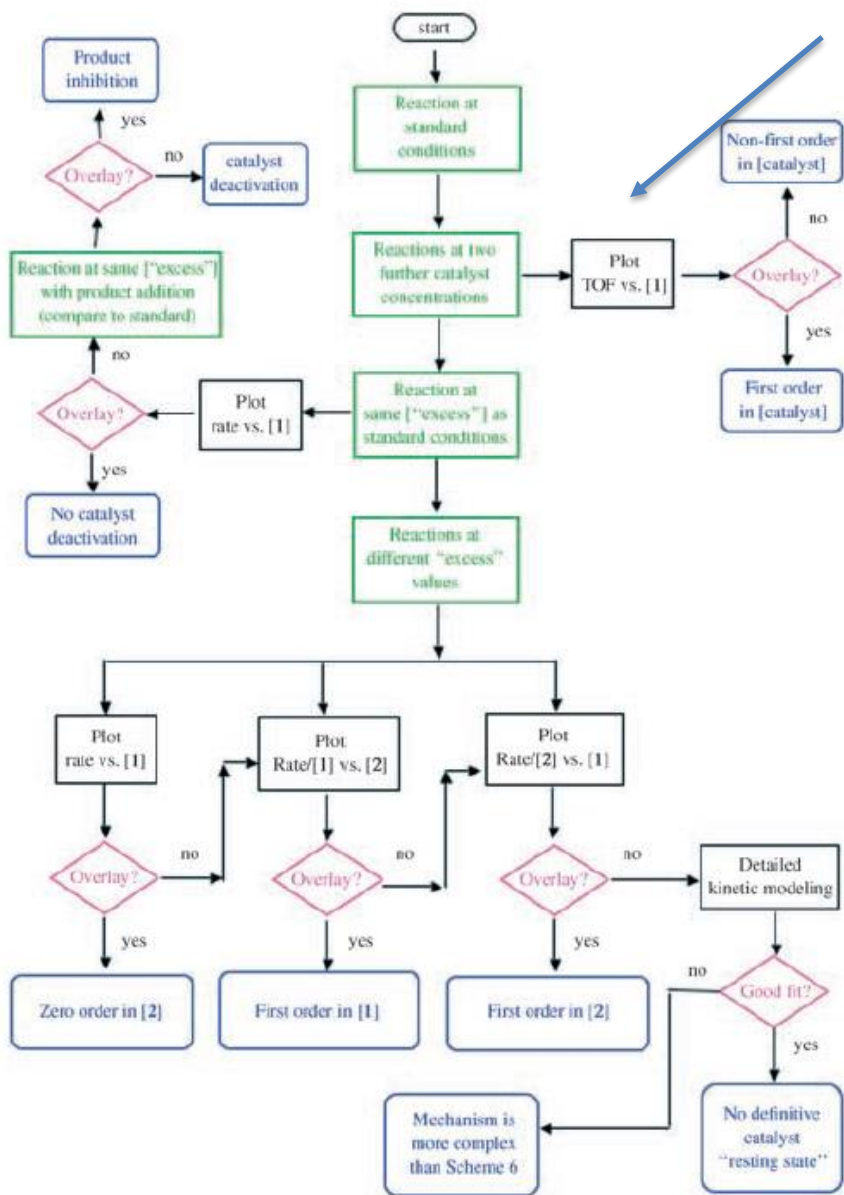
“graphical rate equation”

Determining absolute rates – a brief introduction to RPKA

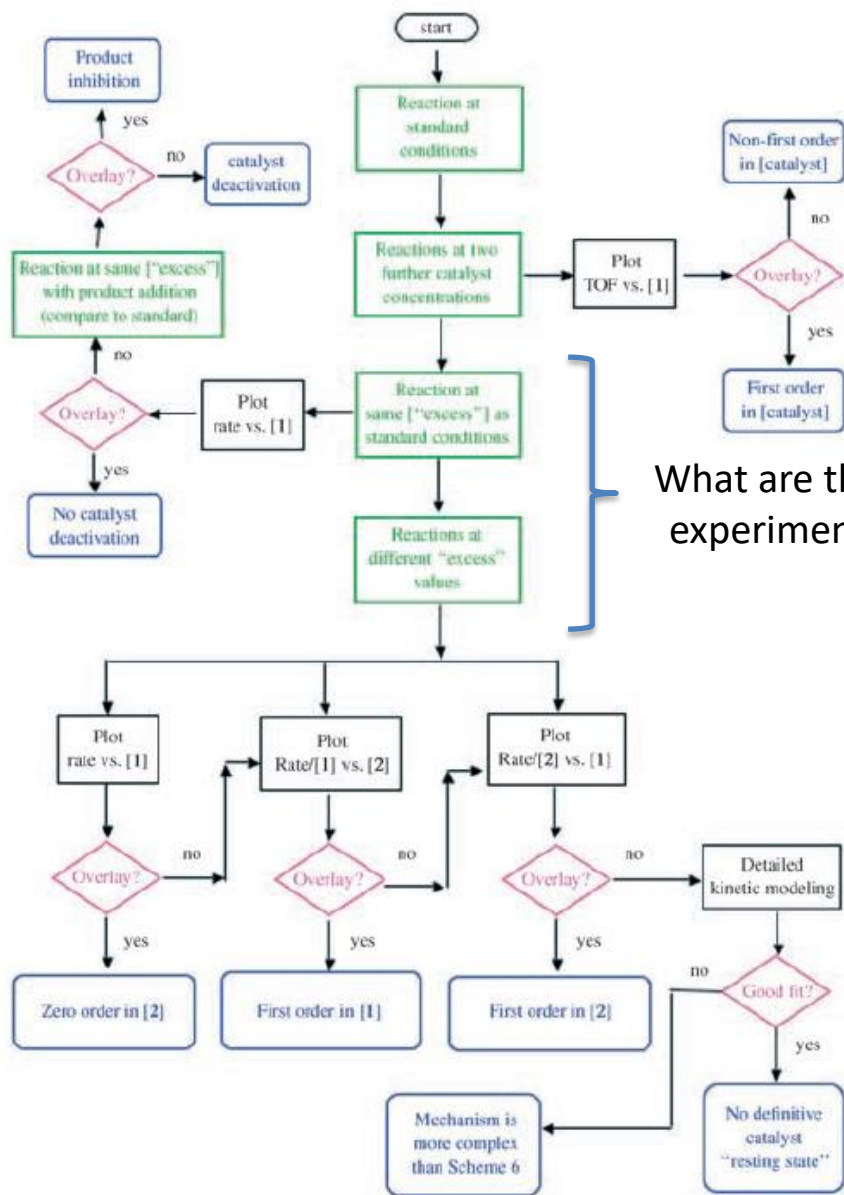


Determining absolute rates – a brief introduction to RPKA

This is the same way we determine catalyst order with initial rates (but we're determining k_{obs} from the full reaction time-course, so it is a bit more accurate)



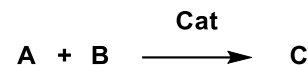
Determining absolute rates – a brief introduction to RPKA



What are these experiments?

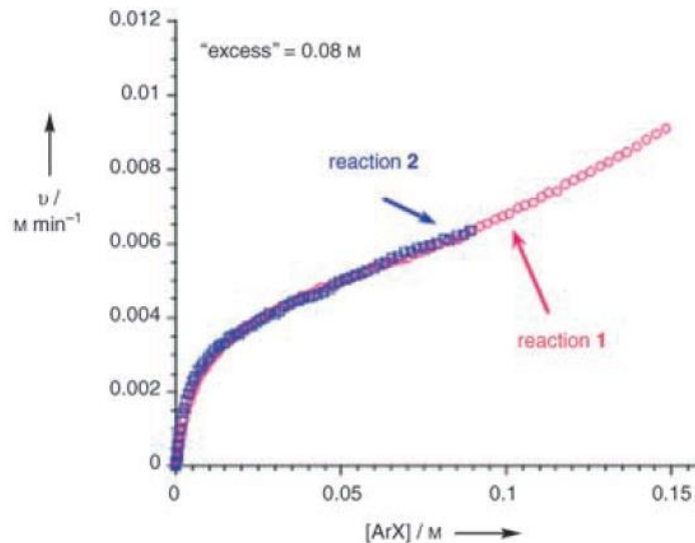
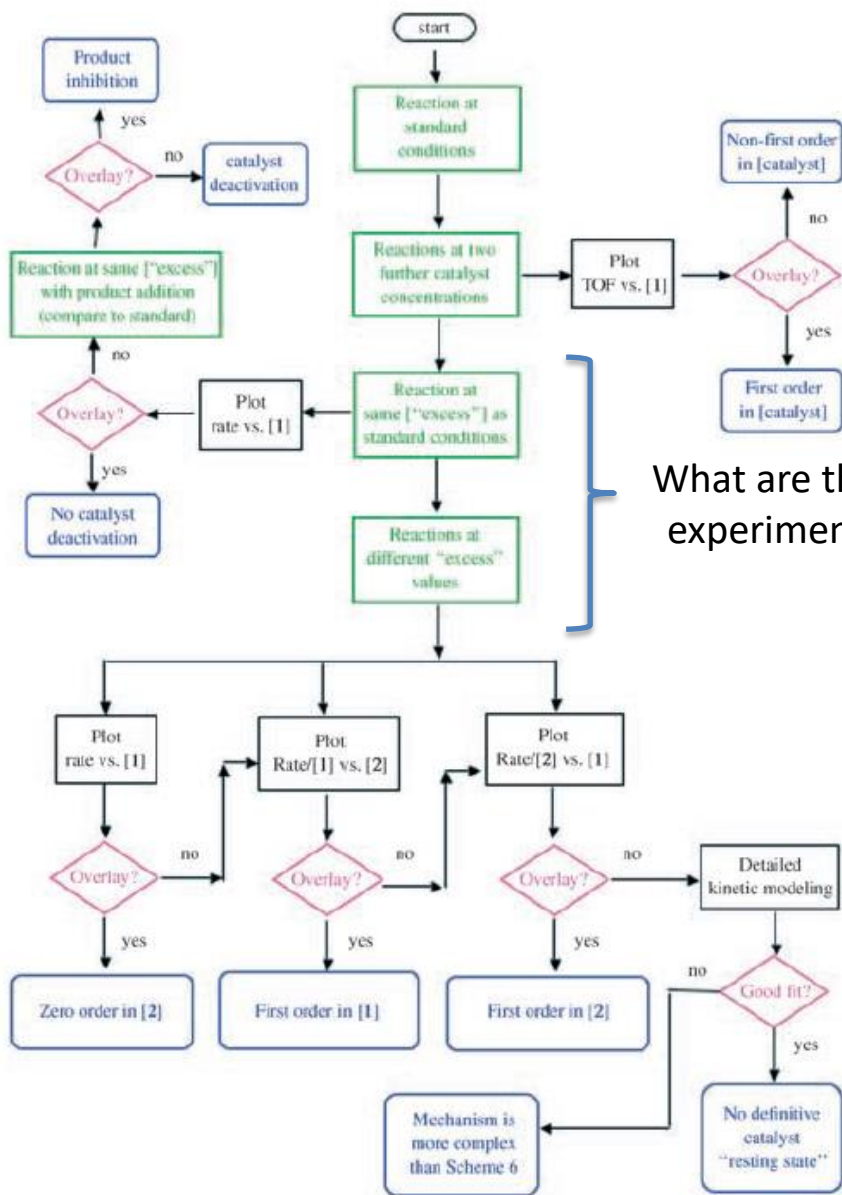
Determining absolute rates – a brief introduction to RPKA

1) The “same excess” experiment



	[A]	[B]	Excess
Rxn 1	0.16	0.24	0.08
Rxn 2	0.12	0.20	0.08
Rxn 1 (after formation of 0.04 mmol of pdt)	0.12	0.20	0.08

What are these experiments?

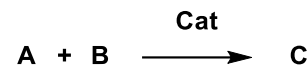


This reaction is kinetically well behaved!*

*apart from the change in RDTs at high conversion

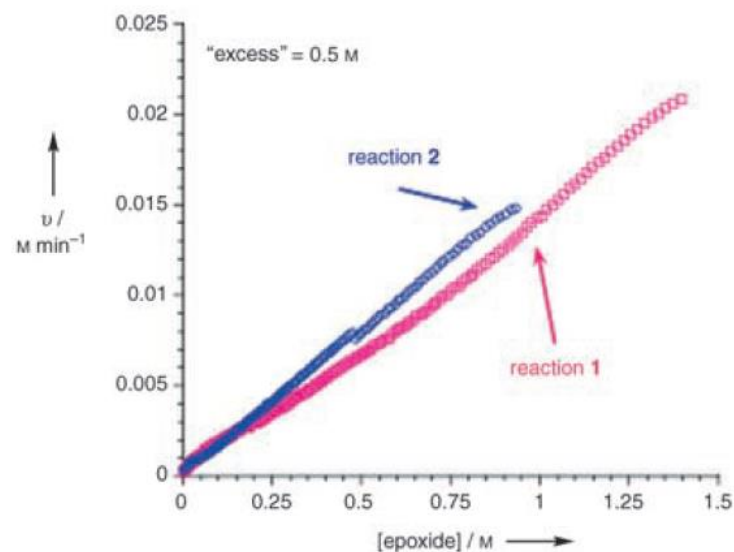
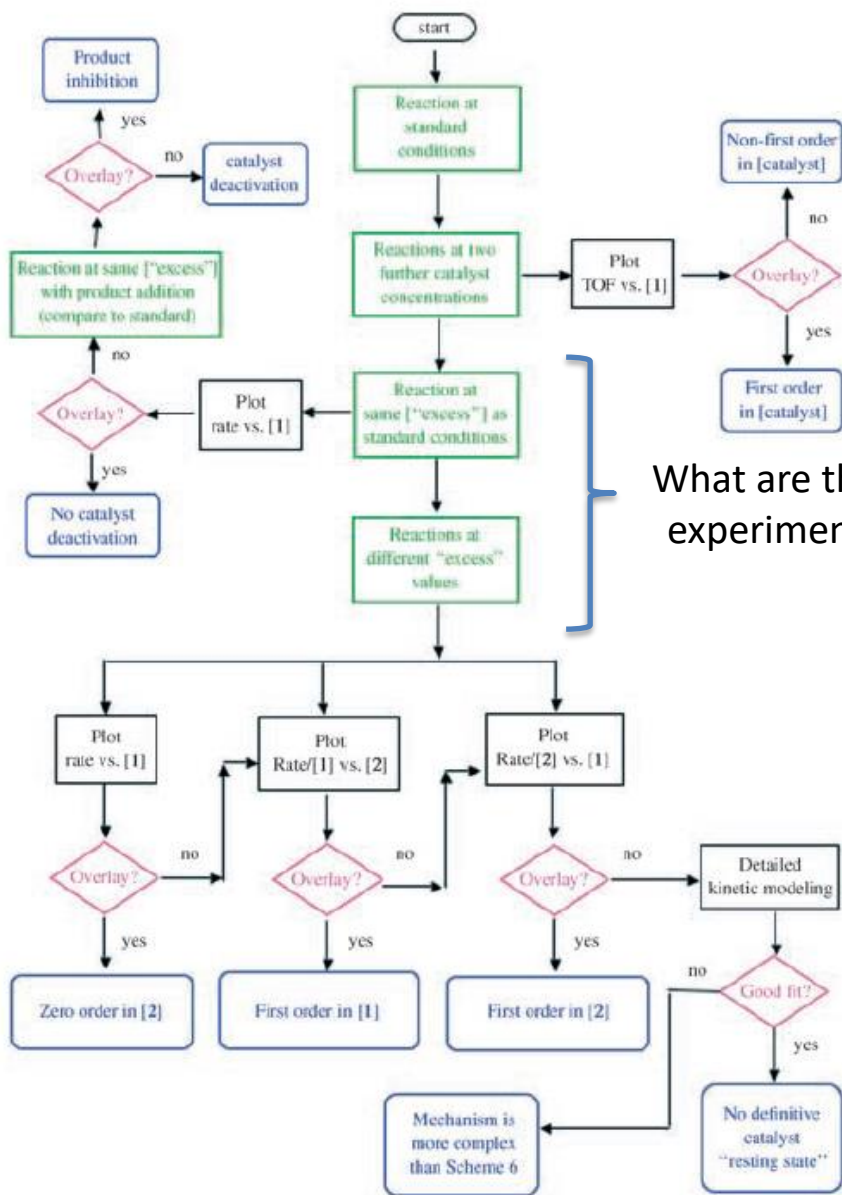
Determining absolute rates – a brief introduction to RPKA

1) The “same excess” experiment



	[A]	[B]	Excess
Rxn 1	1.5	2	0.5
Rxn 2	1	1.5	0.5
Rxn 1 (after formation of 0.5 mmol of pdt)	1	1.5	0.5

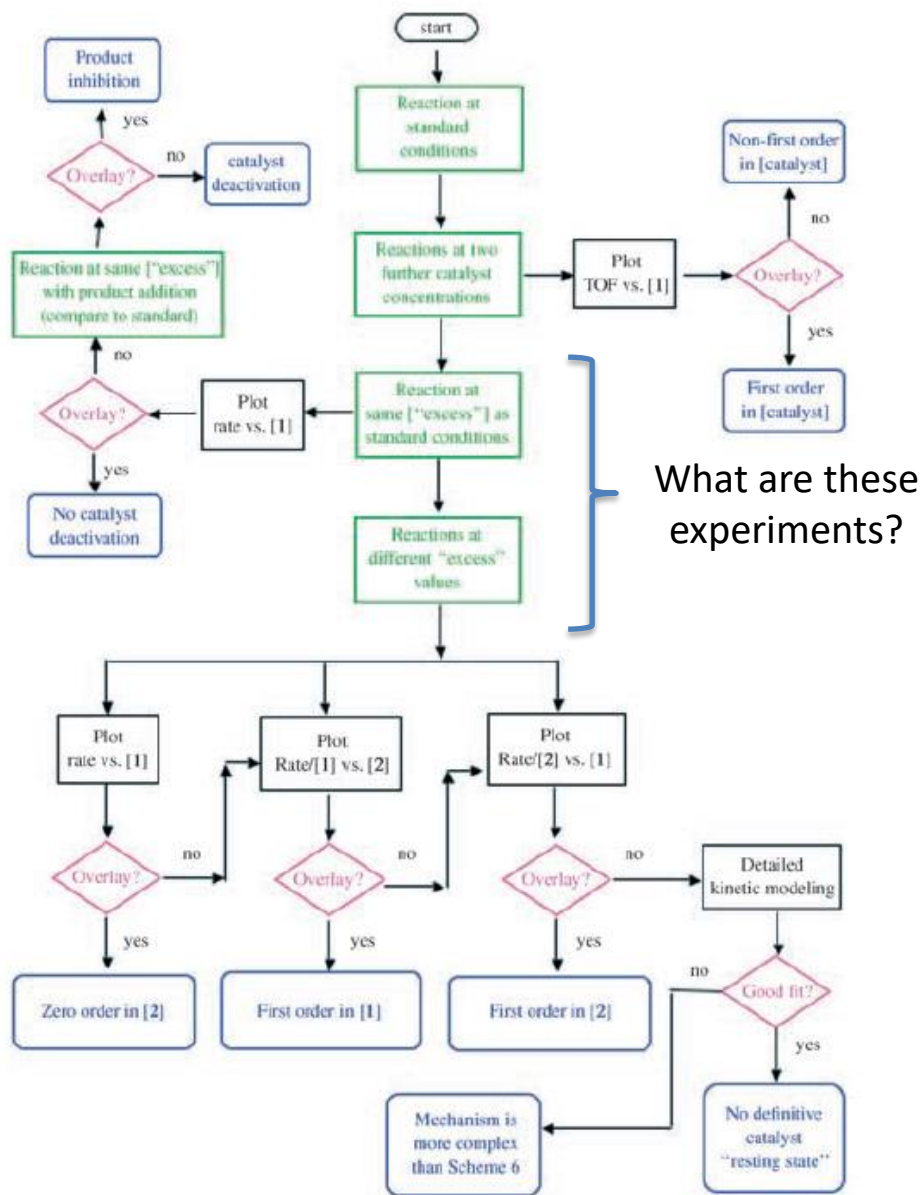
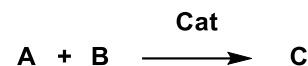
What are these experiments?



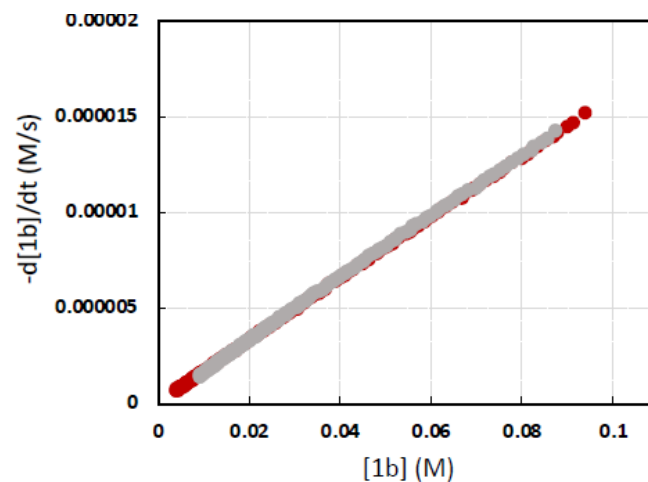
This reaction is not kinetically well behaved!
Cat decomp or pdt inhibition are likely occurring

Determining absolute rates – a brief introduction to RPKA

1) The “different excess” experiment



	[A]	[1b]	Excess
Red	0.115	0.1	0.015
Gray	0.215	0.1	0.115



at identical [1b] (x-axis) but non-identical [A] the rates overlay -> the reaction is 0th order in [A]

Determining absolute rates – summary

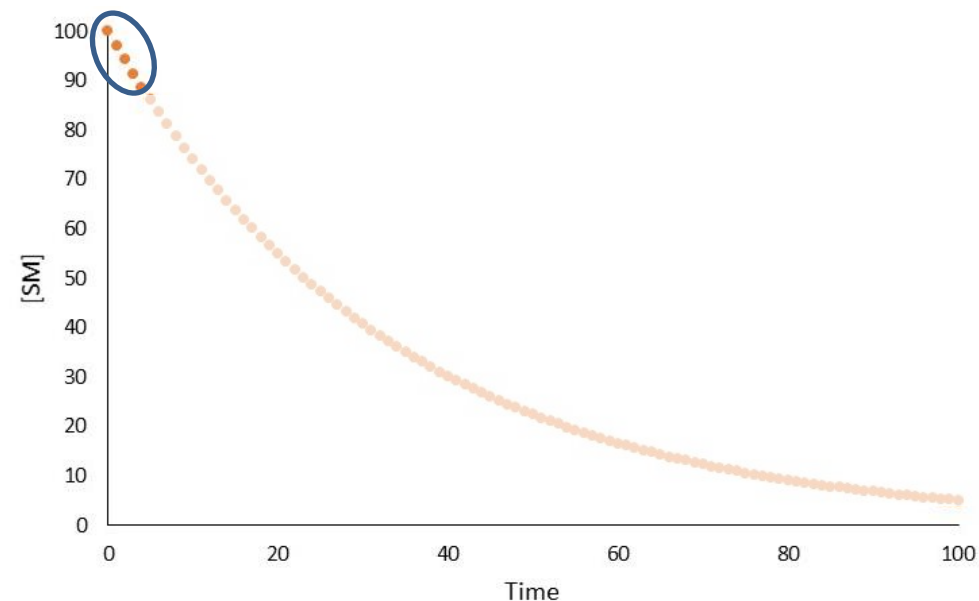
-> conceptually simple

-> generally, the experiments are straightforward
(can use aliquots or parallel reactions)

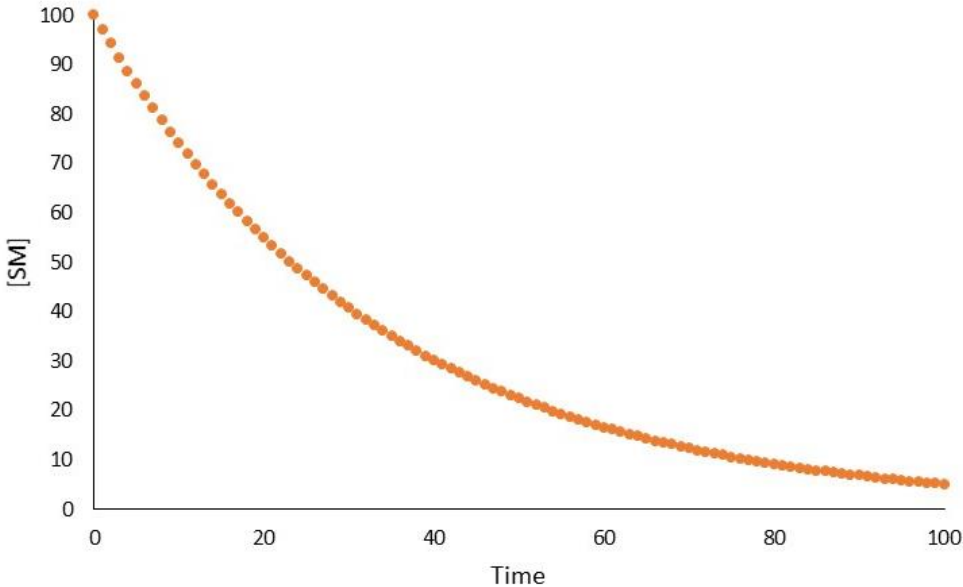
-> requires many experiments/data points
(~25/reagent of interest – this can get really
laborious if you are determining order in multiple
reagents)

-> avoids complications from kinetic misbehavior
(catalyst death and product inhibition should be
minimal within the first 10% of the reaction)

-> blind to kinetic misbehavior



Determining absolute rates – summary



Initial rates and RPKA are largely complimentary techniques: which is best depends on the question(s) you want to ask and the behavior of your particular system, however...

RPKA uses data from a full or nearly full reaction time course (you need at least a few half-lives)

-> conceptually more complicated

-> assay development and experiments can be challenging (requires *in situ* monitoring)

-> requires far fewer experiments, and nearly all of the “cost” is up front in assay development (the marginal labor involved in determining order in an additional reagent is low)

-> any kinetic misbehavior that occurs will confound a “simple” determination of kinetic orders

-> reveals kinetic misbehavior and allows you to study it whether you originally knew to look for it or not

Determining absolute rates – summary

-> conceptually simple

-> generally, the experiments are straightforward
(can use aliquots or parallel reactions)

-> requires many experiments/data points
(~25/reagent of interest – this can get really
laborious if you are determining order in multiple
reagents)

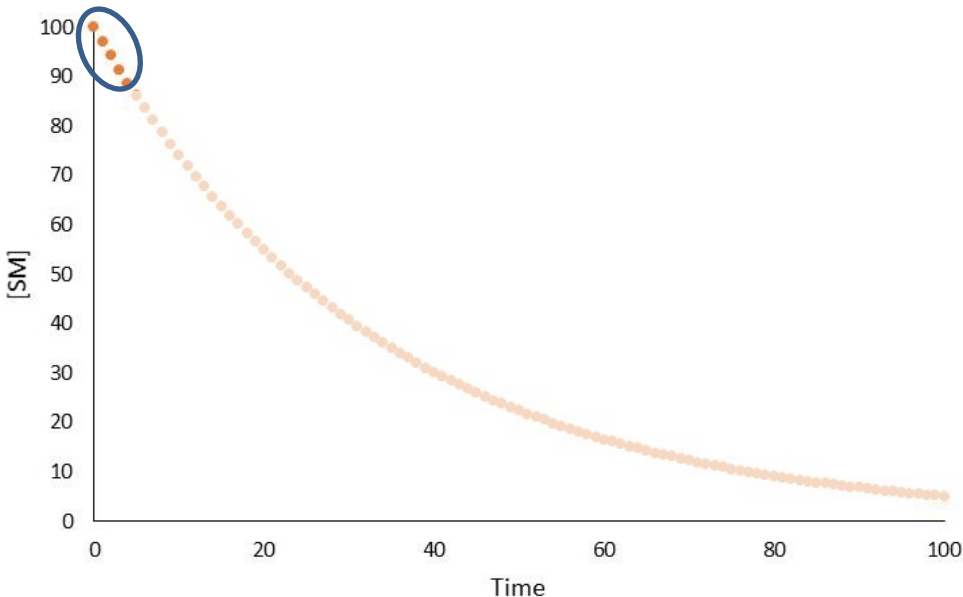
-> avoids complications from kinetic misbehavior
(catalyst death and product inhibition should be
minimal within the first 10% of the reaction)

-> blind to kinetic misbehavior

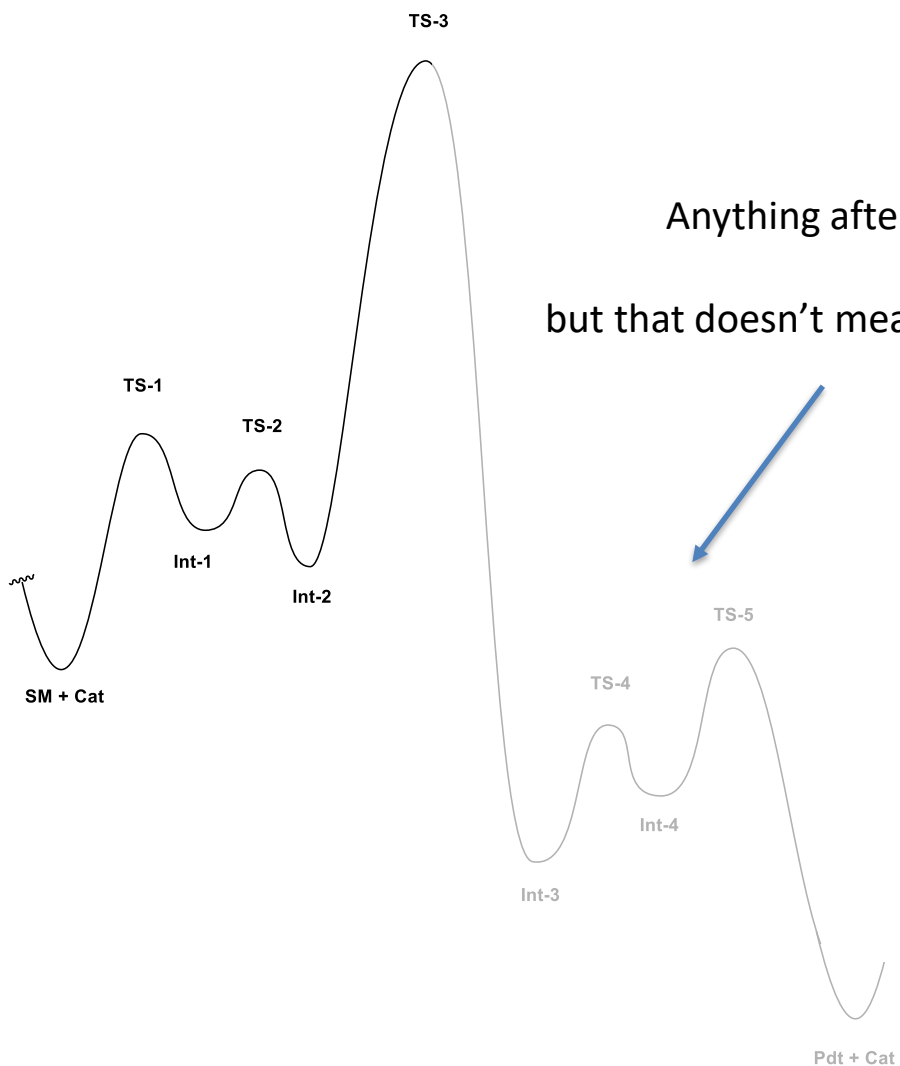
If we are going to do kinetics in our lab, we should probably use initial rates

We would likely be asking a targeted question (e.g., what is my catalyst order), not trying to determine the complete rate law

Our reactions are typically heterogeneous and we know catalyst death is common -> almost certainly are not kinetically well behaved and likely not amenable to *in situ* monitoring



Looking behind the curtain



Anything after the RDTS is invisible to absolute rate kinetics...

but that doesn't mean we can't study them with competition experiments!