

① LECTURE 14

ISOTOPE LABELING
CATALYSIS

PS#6 due Now.
PS#7 due Tues, 10/27.

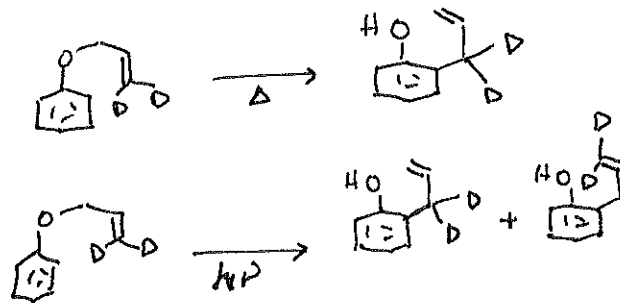
CBI Seminar: Brittany & Sara
Wed, 12:30
206 BRL

*READING: Blackmond. AIE 2005,
44, 4302.

② ISOTOPE LABELING / SCRAMBLING

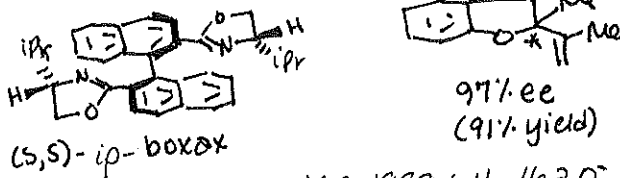
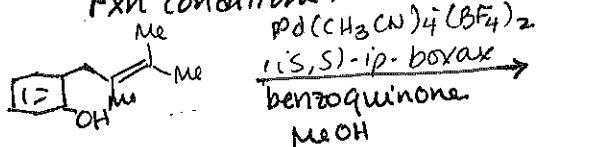
Isotopically label SM & see where isotopes end up in product.

EX: CLAISEN REARRANGEMENT



③ ex: Hayashi et al. JACS 2004, 126, 3036.

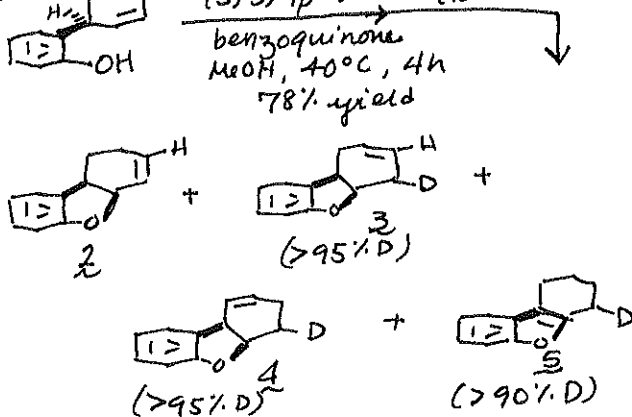
Wacker cyclization: Syn or Anti
oxypalladation? Dependent on
rxn conditions.



JOC 1999, 104, 1620.

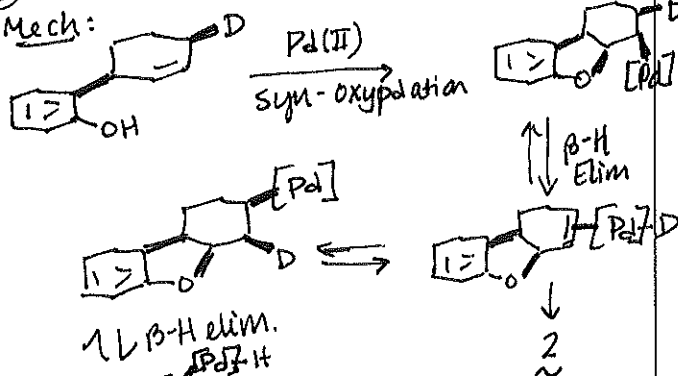
Hard to tell syn vs. anti b/c of β -H
elimination.

④ Expt: Pd(MeCN)₄(BF₄)₂ (5 mol%),
(S,S)-ip-boxax (10 mol%),
benzoquinone,
MeOH, 40°C, 4h
78% yield



↳ Syn oxypalladation.

⑤ Mech:



3

Challenge: Predict
product(s) if
oxypalladation was
anti.

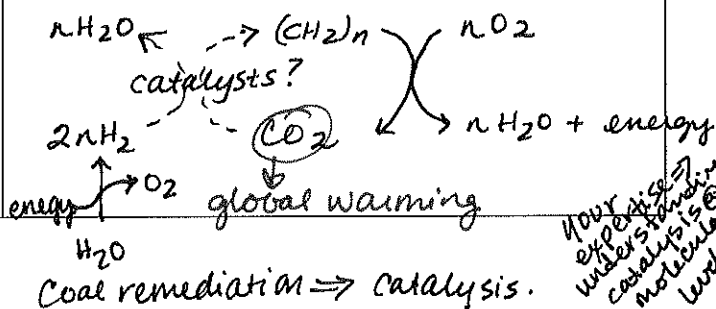
⑥ CATALYSIS

Why should you care?

Catalysis is important
in pharmaceuticals, medicines,
health.

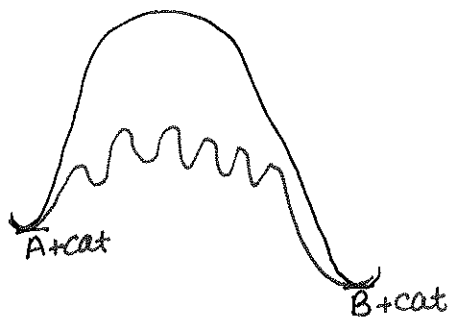
Also → Biology / Enzymes

Also → Energy. HUGE PROBLEM/
OPPORTUNITY.



How else?
expensive?
wider variety
catalysis
molecular
level.

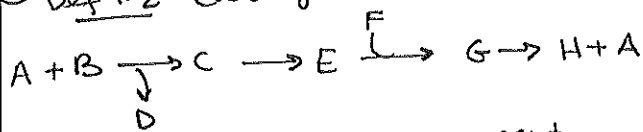
⑦ What is catalysis?



Def #1: $\frac{k_{cat}}{k_{uncat}} > 1$ (no change in thermodynamics)

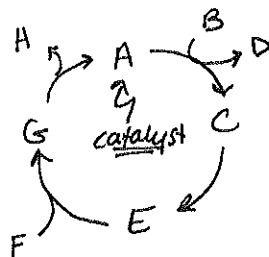
Is heat a catalyst? No.
Agency of a molecule to lower energy barrier.

⑧ Def #2: Catalyst doesn't change.



If $B \rightarrow H$ is faster w/ A present, A = catalyst.

Represent on a catalytic cycle...



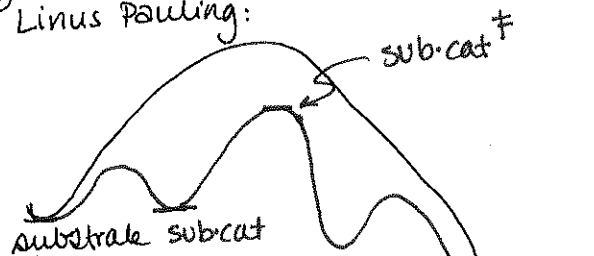
Everything involving catalyst goes in the circle (catalytically present).

Everything else (stoichiometric reactants & prod) go outside.

⑨ What if A makes $B \rightarrow H$ slower?

Matter of definition, but we generally only care abt catalysts that speed it up.

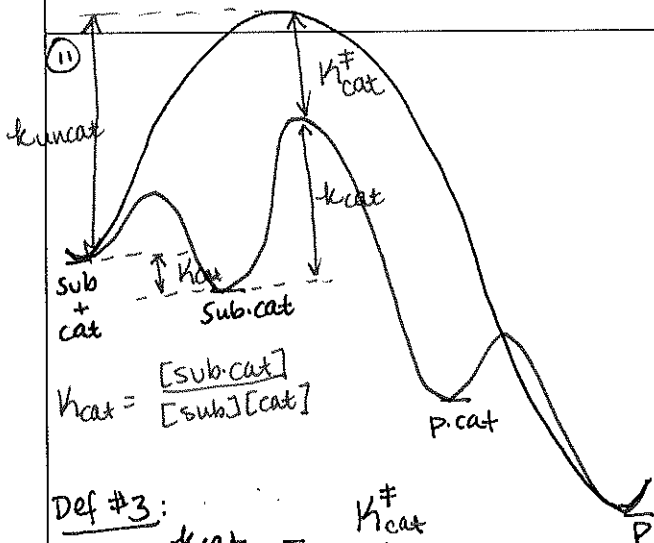
⑩ Linus Pauling:



Differential binding of TS & substrate.

Catalyst stabilizes TS more than it stabilizes substrate.

Does cat have to bind substrate?
Yes. (it would never find a TS)

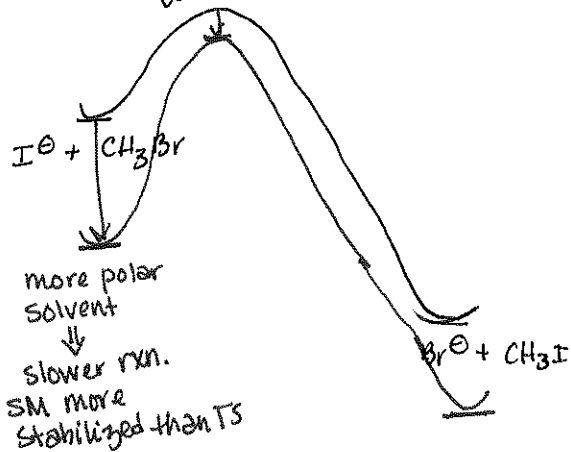


$$k_{cat} = \frac{[sub \cdot cat]}{[sub][cat]}$$

Def #3:
 $1 < \frac{k_{cat}}{k_{uncat}} = \frac{K_{cat}^{\#}}{K_{cat}}$

Binding to TS stronger than binding to SM.

⑫ Solvent effect on S_N2 :



more polar solvent
 \downarrow
slower rxn.

SM more stabilized than TS

Is less polar solvent a catalyst?
Not really \rightarrow Not substoichiometric.

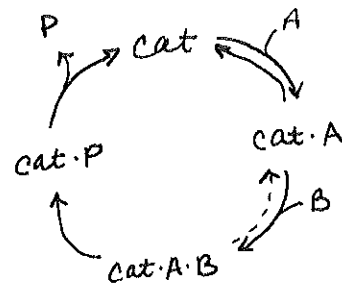
13

Def #4: Substoichiometric rxn accelerator relative to reactants.
* More a practical definition than fundamental.

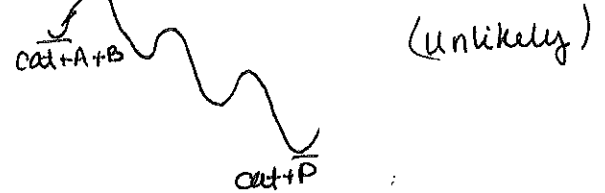
Brings up

TURNOVER - catalyst can & does repeat catalytic cycle.

14 Kinetics of Catalytic cycle

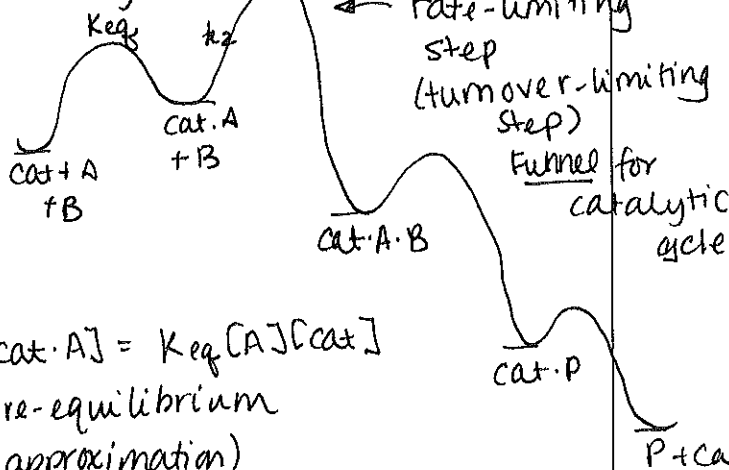


Possibility #1: All steps irreversible:



15

Possibility #2: Reversible steps (likely)



$$[cat \cdot A] = K_{eq} [A][cat]$$

(pre-equilibrium approximation)

16

$$rate = k_2 [cat \cdot A][B]$$

$$rate = k_2 K_{eq} [A][B][cat]$$

Seems like same treatment as we gave stoichiometric reagents...

17

But...

- 1) Changes in $[A]$ & $[B]$ over rxn course \Rightarrow Change in rds.
- 2) May not have a clearly defined rate-limiting step...

Biology / Enzymes (Evolutionary Pressure)
Jeremy Knowles \Rightarrow Perfect Catalyst

- 1) Catalyst reacts as fast as it can.
- 2) All steps are as fast as they can be & abt the same height.

18

ex: Triose phosphate isomerase (knowles *ACIE* 1977, 16, 285).

Diffusion controlled \rightarrow every time substrate hits enzyme, rxn occurs.

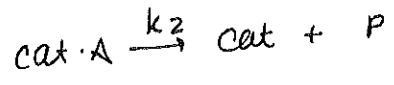
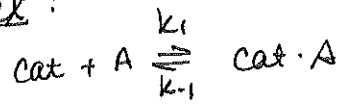
Amazing!!
(Flow control)

Almost impossible in a flask \rightarrow Not as long to evolve. Not flow-controlled

(concentrations change).
Need to look at whole cycle.

19

ex:



$$\text{rate} = k_2 [\text{cat} \cdot \text{A}]$$

What is [cat·A]?

$$\text{SSA: } \frac{d[\text{cat} \cdot \text{A}]}{dt} = 0 = k_1 [\text{cat}][\text{A}] - k_{-1} [\text{cat} \cdot \text{A}] - k_2 [\text{cat} \cdot \text{A}]$$

$$[\text{cat} \cdot \text{A}] = \frac{k_1 [\text{cat}][\text{A}]}{k_{-1} + k_2}$$

20

$$\text{rate} = v = \frac{d[\text{P}]}{dt} = \frac{k_1 k_2 [\text{cat}][\text{A}]}{k_{-1} + k_2}$$

Amount of catalyst not bound to A.

How do we know [cat]???

21

what we put in the flask.

$$[\text{cat}]_T = [\text{cat}] + [\text{cat} \cdot \text{A}]$$

$$[\text{cat}] = [\text{cat}]_T - [\text{cat} \cdot \text{A}]$$

$$k_2 [\text{cat} \cdot \text{A}] = \frac{k_1 k_2 [\text{A}] ([\text{cat}]_T - [\text{cat} \cdot \text{A}])}{k_{-1} + k_2}$$

$$k_2 [\text{cat} \cdot \text{A}] = \frac{k_1 k_2 [\text{A}] [\text{cat}]_T}{k_{-1} + k_2} - \frac{k_1 k_2 [\text{cat} \cdot \text{A}] [\text{A}]}{k_{-1} + k_2}$$

$$k_2 [\text{cat} \cdot \text{A}] + \frac{k_1 k_2 [\text{cat} \cdot \text{A}] [\text{A}]}{k_{-1} + k_2} = \frac{k_1 k_2 [\text{A}] [\text{cat}]_T}{k_{-1} + k_2}$$

$$k_2 [\text{cat} \cdot \text{A}] \left(1 + \frac{k_1 k_2 [\text{A}]}{k_{-1} + k_2} \right) = \frac{k_1 k_2 [\text{A}] [\text{cat}]_T}{(k_{-1} + k_2)}$$

22

23

$$[\text{cat} \cdot \text{A}] = \frac{k_1 [\text{A}] [\text{cat}]_T}{(k_{-1} + k_2) \left(1 + \frac{k_1 k_2 [\text{A}]}{k_{-1} + k_2} \right)}$$

Plug into rate eqn:
 catalytic term $(k_1 k_2 [\text{A}] [\text{cat}]_T)$
 potential term $(k_{-1} + k_2)$

$$v = \frac{(k_1 k_2 [\text{A}] [\text{cat}]_T)}{(k_{-1} + k_2) \left(1 + \frac{k_1 k_2 [\text{A}]}{k_{-1} + k_2} \right)}$$

absorption term \equiv expression of where catalyst can be.
 naked catalyst \rightarrow cat·A

"1+ FORM AT"
 Describes ALL catalytic rxns.

24

General Form:

$$v = \frac{C_1 [\text{cat}]_T [\text{A}]}{1 + C_2 [\text{A}]}$$

Michaelis-Menton in different form.
 $\text{E} \rightleftharpoons \text{E} \cdot \text{S} \xrightarrow{k_{\text{cat}}} \text{P}$

Michaelis-Menton:

$$\text{rate} = \frac{k_2 [\text{cat}]_T [\text{A}]}{\frac{k_{-1} + k_2}{k_1} + [\text{A}]} = v = \frac{k_{\text{cat}} [\text{E}] [\text{S}]}{K_m + [\text{S}]}$$

E = enzyme
 S = substrate
 k_{cat} = rate constant for catalyst (fastest possibility)

K_m = Michaelis constant
 \hookrightarrow Dissociation constant for E·S

25

What we just did:
Pre-equilibrium approximation

$$[cat \cdot A] = \frac{k_1}{k_{-1}} [cat][A]$$

Assumes $k_2 \ll k_{-1}$.

(Note: SSA is a more complete representation.)

26

M-M Denominator:
Limiting Scenarios:

1) $[S] \gg K_m$

$$v = \frac{k_{cat} [E][S]}{[S]} = k_{cat} [E]$$

$$= v_{max}$$

fastest enzyme can go

27

2) $[S] \ll K_m$

$$v = \frac{k_{cat} [E][S]}{K_m}$$

$\frac{k_{cat}}{K_m} \Rightarrow$ measure of catalyst efficiency

$10^8 - 10^{10}$ for perfect catalyst.
(diffusion controlled).

28

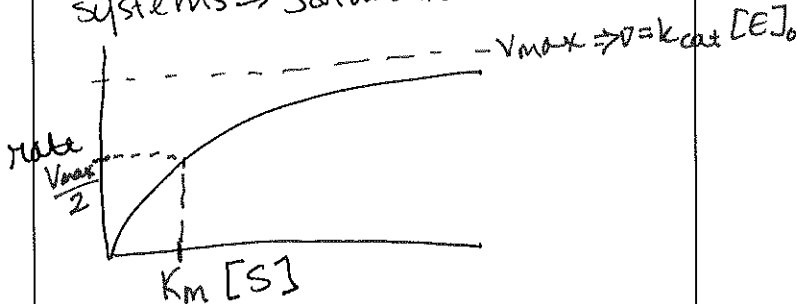
3) $[S] = K_m$

$$v = \frac{k_{cat} [E][S]}{K_m + [S]} = \frac{k_{cat} [E][S]}{2[S]}$$

$$= \frac{1}{2} v_{max}$$

29

Can plot Michaelis-Menton systems \Rightarrow Saturation Curve.



But curve may make you nervous...

30

3 different ways to plot:

1) Lineweaver-Burk

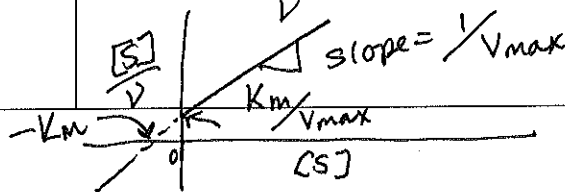
$\frac{1}{v}$ vs. $\frac{1}{[S]}$ (minimizes experimental error)
Makes bad data look good.

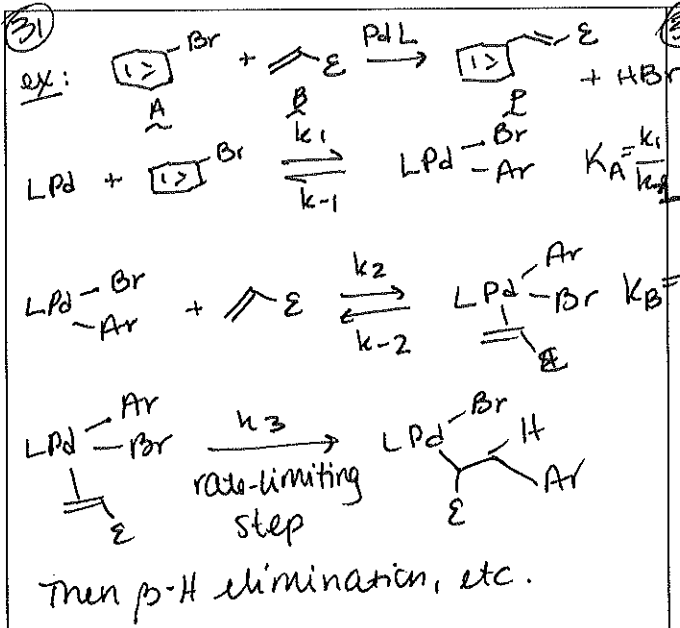
2) v vs. $\frac{v}{[S]}$ Eadie-Hofstee

Makes good data look bad.

3) Hanes-Woolf (fair way to plot)

$\frac{[S]}{v}$ vs. $[S]$





32) Apply "1+" Eq'n:

$$\text{rate} = \frac{K_A K_B k_3 [A][B][\text{cat}]_{\text{tot}}}{1 + K_A [A] + K_A K_B [A][B]}$$

naked cat·A cat·A·B

(Assumed cat·P is not a significant term)

33) Issues w/ Catalytic Rxns:

- Catalyst funny business ...
- Catalyst dies
- Solvent polarity changes over rxn course
- Prod inhibition
- etc.

Must determine if catalyst is "well-behaved."

34) Check for "well-behaved" catalyst:

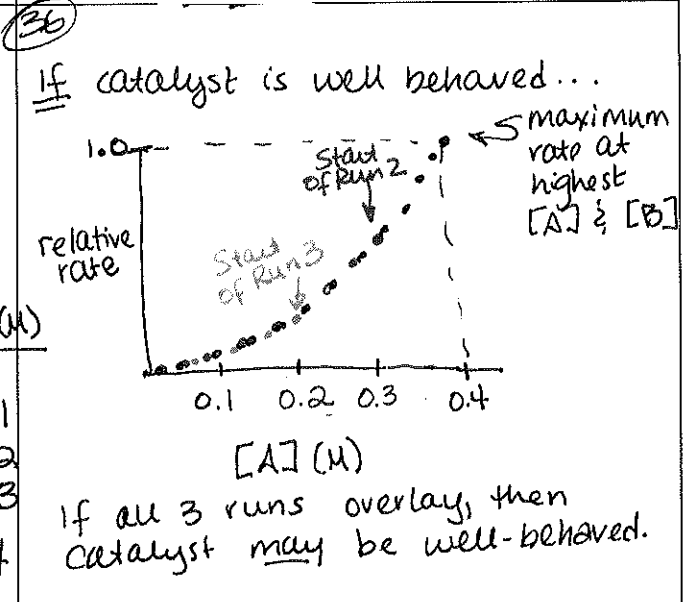
"Same Excess Experiment"

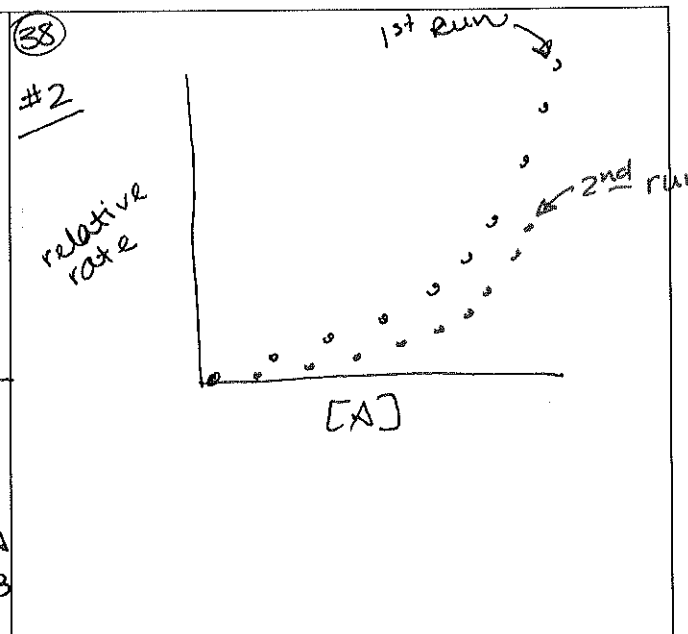
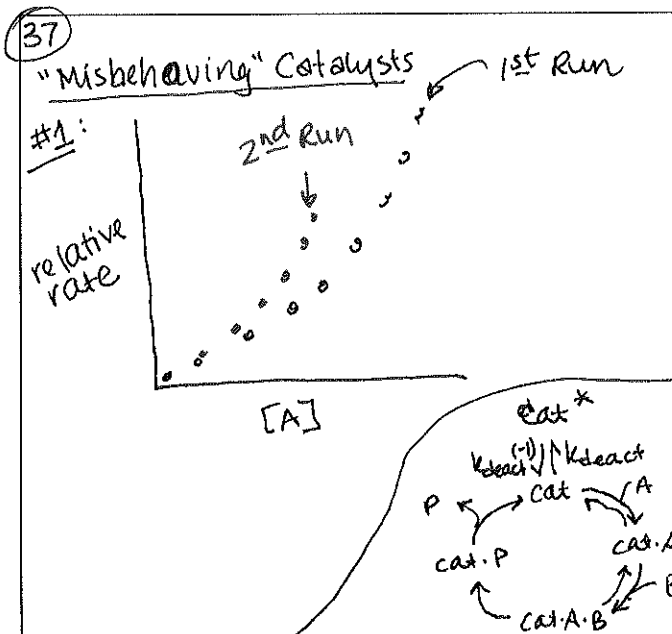
- 1) $[\text{cat}]_{\text{total}}$ same. $A + B \xrightarrow{\text{cat}} P$
- 2) Excess of B over A same.
- 3) Different $[B]_0$ & $[A]_0$
- 4) Plot $\frac{\text{relative rate}}{[A]}$ vs. $[A]$

35)

Kinetic Run	$[\text{cat}]_i (\text{M})$	$[A]_i (\text{M})$	$[B]_i (\text{M})$
1	0.01	0.4	0.5
2	0.01	0.3	0.4
3	0.01	0.2	0.3

% conv of A	$[\text{cat}] (\text{M})$	$[A] (\text{M})$	$[B] (\text{M})$	$[P] (\text{M})$
Run 1 → 0	0.01	0.4	0.5	0
Looks like Start of Run 2 → 25	0.01	0.3	0.4	0.1
Looks like Start of Run 3 → 50	0.01	0.2	0.3	0.2
75	0.01	0.3	0.2	0.3
100	0.01	0	0.1	0.4





39 Detectable(?) Scenarios

$$\text{cat} + \text{A} + \text{B} \xrightarrow{k_{\text{cat}}} \text{P} + \text{cat}$$

$$\text{cat} \xrightleftharpoons[k_{-1\text{deact}}]{k_{\text{deact}}} \text{cat}^*$$

Scenario	Detectable?
$k_{\text{deact}} \ll k_{\text{cat}}$	yes
$k_{\text{deact}} \sim k_{\text{cat}}$	yes
$k_{\text{deact}(-1)} \ll k_{\text{cat}}$	yes
$k_{\text{deact}} \sim k_{\text{cat}}$	yes
$k_{\text{deact}(-1)} \sim k_{\text{cat}}$	yes

Handwritten note: catalyst slowly falls out of cat. cycle.

40

Scenario	Detectable
$k_{\text{deact}} \gg k_{\text{cat}}$ $k_{\text{deact}(-1)} \ll k_{\text{cat}}$	No Pd+ (stuck @ dead catalyst)
$k_{\text{deact}} \gg k_{\text{cat}}$ $k_{\text{deact}(-1)} \gg k_{\text{cat}}$	<u>NO</u>

rate = $\frac{C_1[\text{A}][\text{B}][\text{cat}]_T}{1 + C_2[\text{A}] + C_3[\text{A}][\text{B}] + K_{\text{dead}}}$

