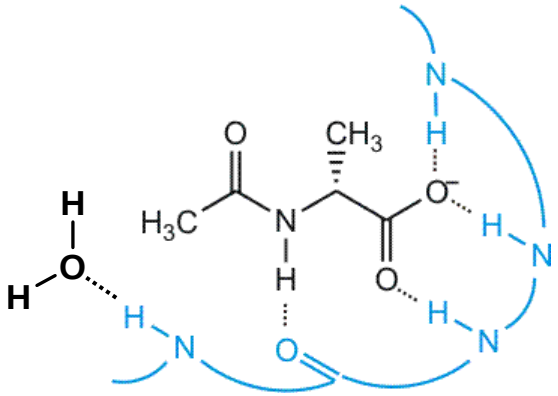
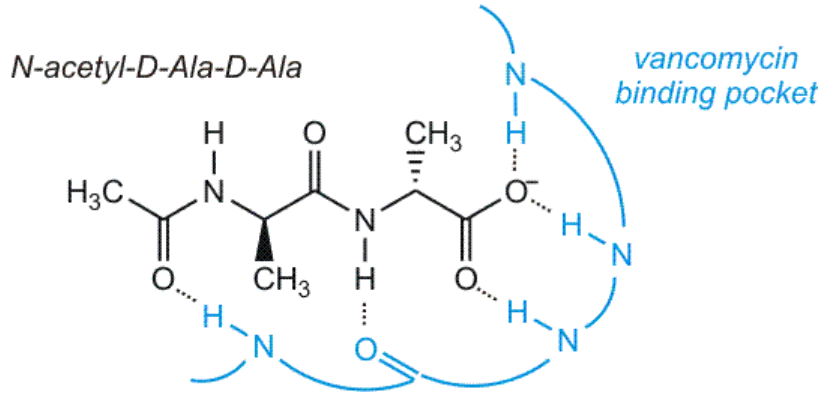
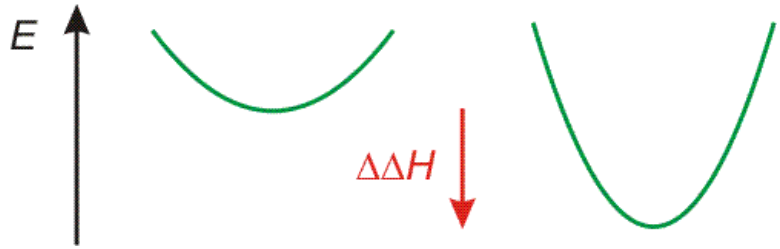
Enthalpy-Entropy Compensation



- Strategy of adding binding groups to increase ligand affinity works.
- But, for additive weak interactions, increased binding enthalpy is compensated by decreased entropy.

$\Delta\Delta H_a$ = -1.5 kcal/mol
$T\Delta\Delta S_a$ = -1.0 kcal/mol





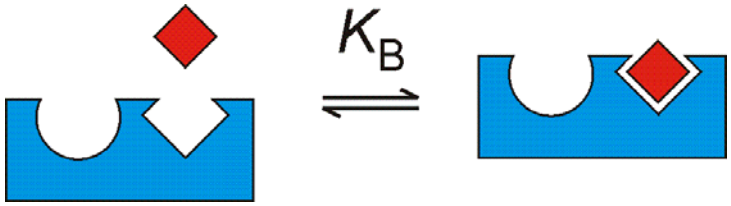
…but thermal energy within deeper potential well doesn't sample as many conformations; so, entropy lost.

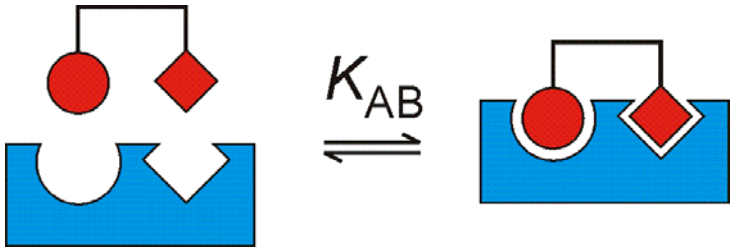
Multiple Interactions ("Multivalency"): Building Better Ligands & Catalysts

Possible reasons for designing/understanding multiple interactions:

- Stronger binders
  - Higher-affinity pharmaceuticals
  - Improved organometallic ligands
- More selective binders
  - Decrease non-specific drug targeting
  - Improved response of analytical detectors
- Faster catalysts
  - Better-designed synthetic enzymes
  - Improved polymerization catalysts
- More selective catalysts
  - Enhanced enantioselectivity, substrate specificity

Multivalency ("Chelate Effect"): Concepts



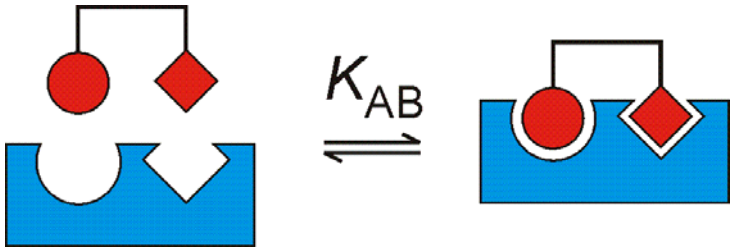


What is the advantage of tethering two ligands together?

(sequential step 1 & step 2 above)

$K_{AB} \neq K_A K_B$;
difference illustrates advantage/ disadvantage of connecting ligands.
Effect is primarily *entropic*.

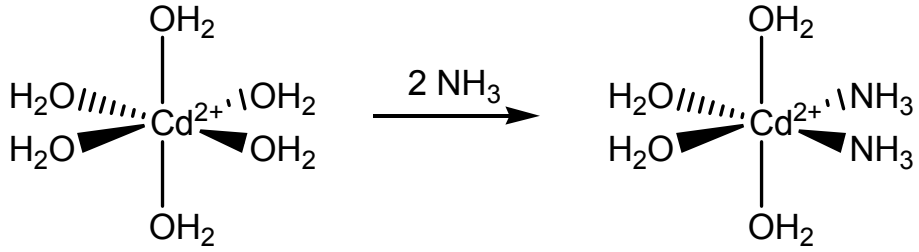
Degree of Cooperativity (α)



What is the advantage of tethering two ligands together?
i.e., How much better or worse does the "**B**" in **A**-**B** bind than you would expect?

$$\alpha = \frac{K_{AB}}{K_A K_B}$$

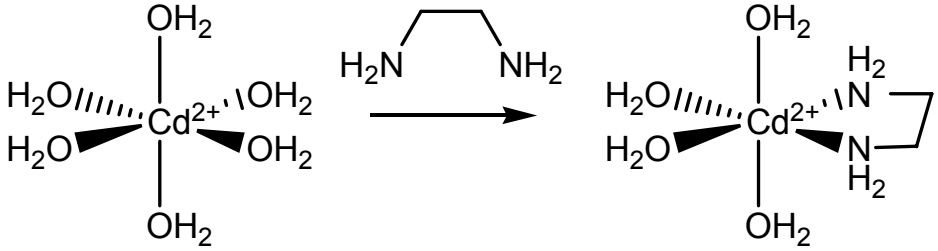
Example:



(because A & B are the same)

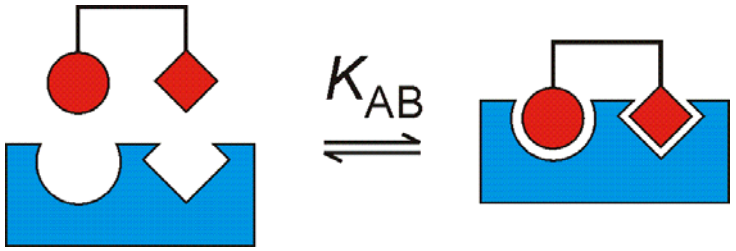
$$K_A K_B = (K_A)^2 = 2.5 \times 10^5\ M^{-2}$$

α = 9.5



$$K_{AB} = 2.4 \times 10^6\ M^{-1}$$

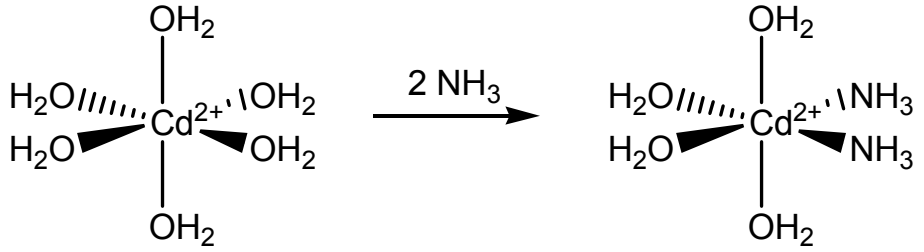
Degree of Cooperativity (α)

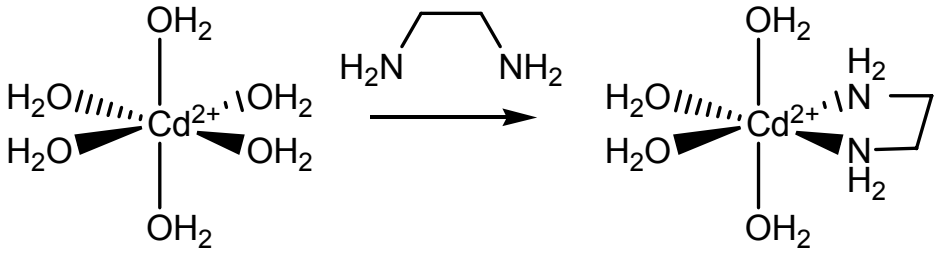


What is the advantage of tethering two ligands together?

$$\alpha = \frac{K_{AB}}{K_A K_B}$$

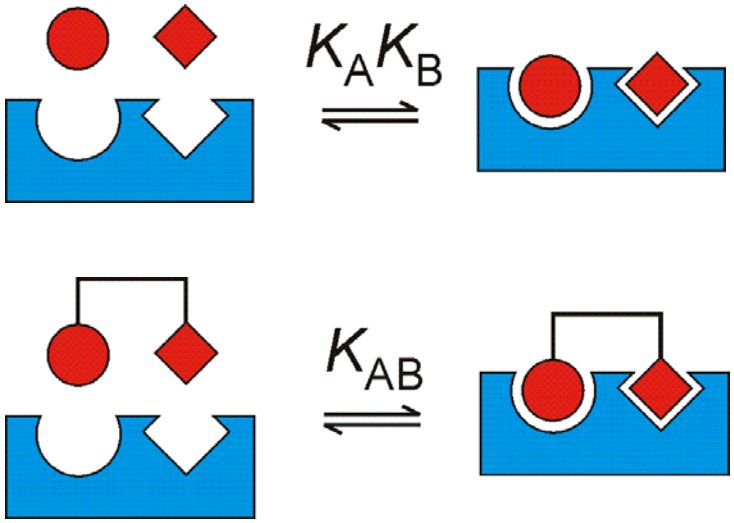
Example:





	$\Delta G°$ (kcal/mol)	$\Delta H°$ (kcal/mol)	$T\Delta S°$ (kcal/mol)
	-6.75	-7.12	-0.37
	-7.96	-7.03	+0.93

Degree of Cooperativity (α)

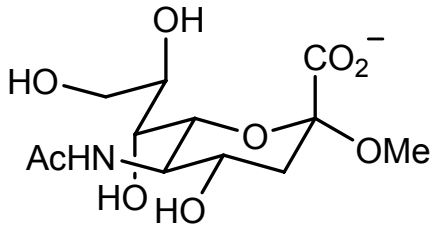


Works well for very small ligands with little conformational freedom.

Works less well with larger ligands.

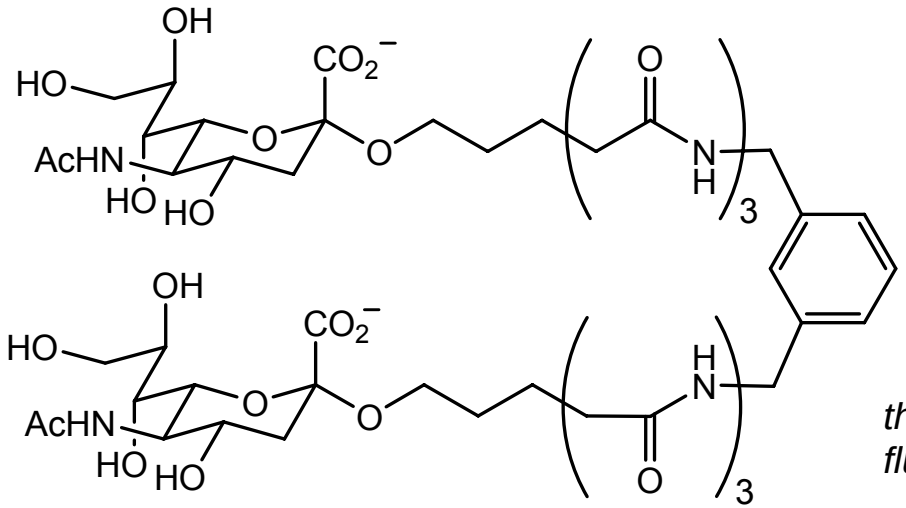
Example:

Influenza hemagglutinin protein. Binds multiple sialic acid molecules on your cells at once.



$K_{\text{sialic acid}} = 400\ M^{-1}$

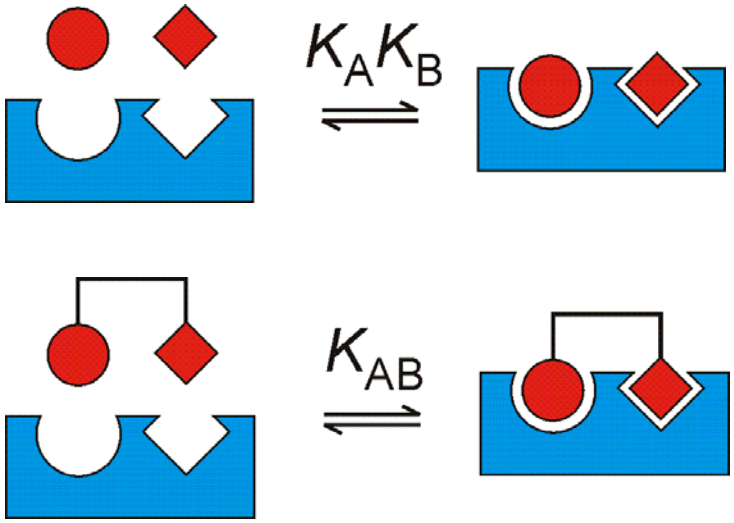
α = 0.25



therapeutic flu inhibitor

$K_{\text{sialic dimer}} = 40000\ M^{-1}$

Degree of Cooperativity (α)

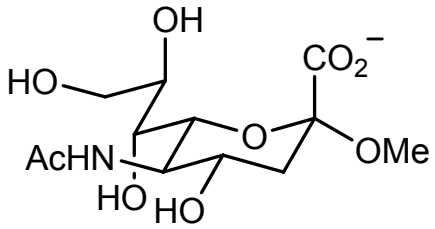


Works well for very small ligands with little conformational freedom.

Works less well with larger ligands.

Example:

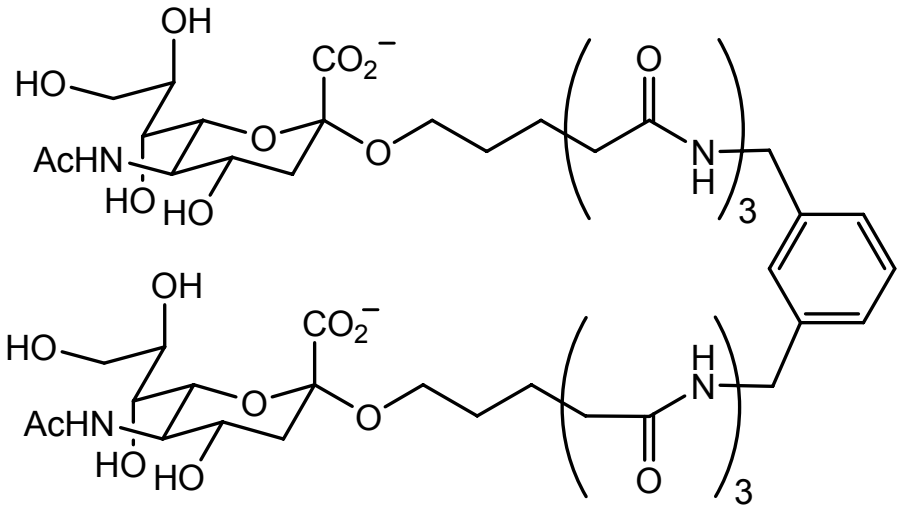
Influenza hemagglutinin protein. Binds multiple sialic acid molecules on your cells at once.



$\Delta G_{\text{sialic acid}}$ = -3.3 kcal/mol

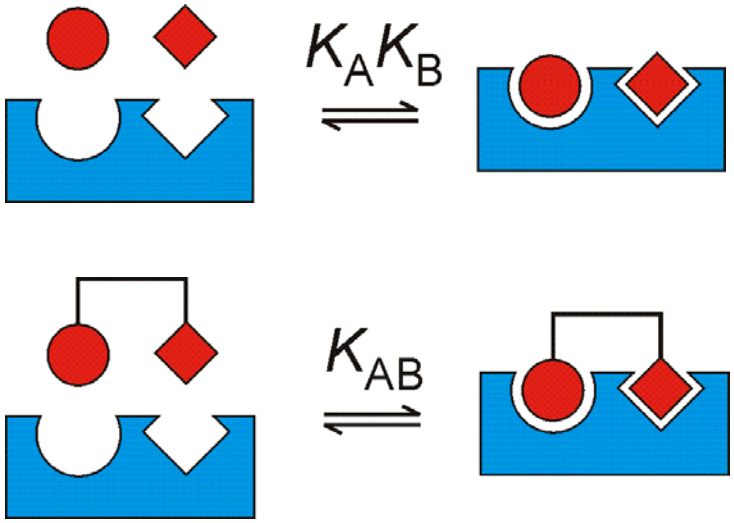
α = 0.25

($\Delta\Delta G$ = +0.8 kcal/mol)



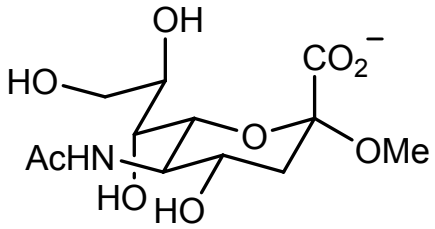
$\Delta G_{\text{sialic dimer}}$ = -5.8 kcal/mol

Enhancement Factor (β)

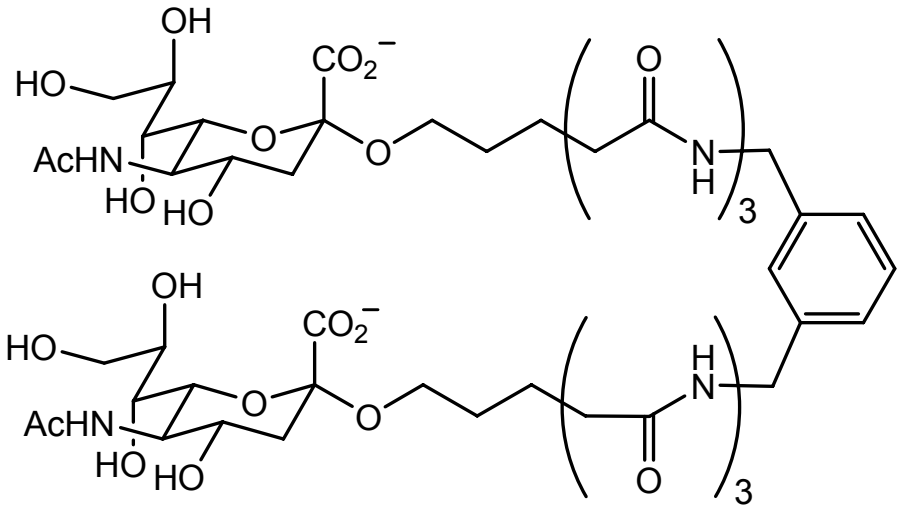


α is a bit unfair for multivalent pharmaceuticals;

Even though Δ*G* values aren't additive, divalent molecule still a better ligand for influenza than monovalent.



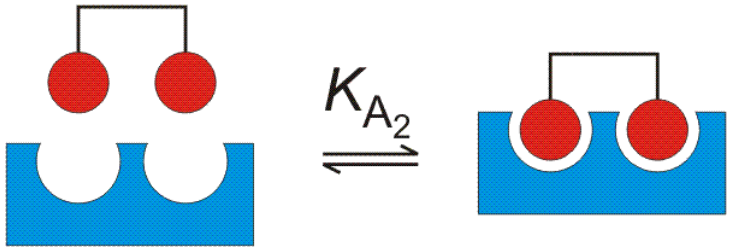
$\Delta G_{\text{sialic acid}}$ = -3.3 kcal/mol



($\Delta\Delta G$ = +0.8 kcal/mol)

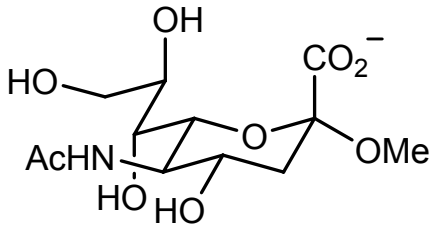
$\Delta G_{\text{sialic dimer}}$ = -5.8 kcal/mol

Enhancement Factor (β)



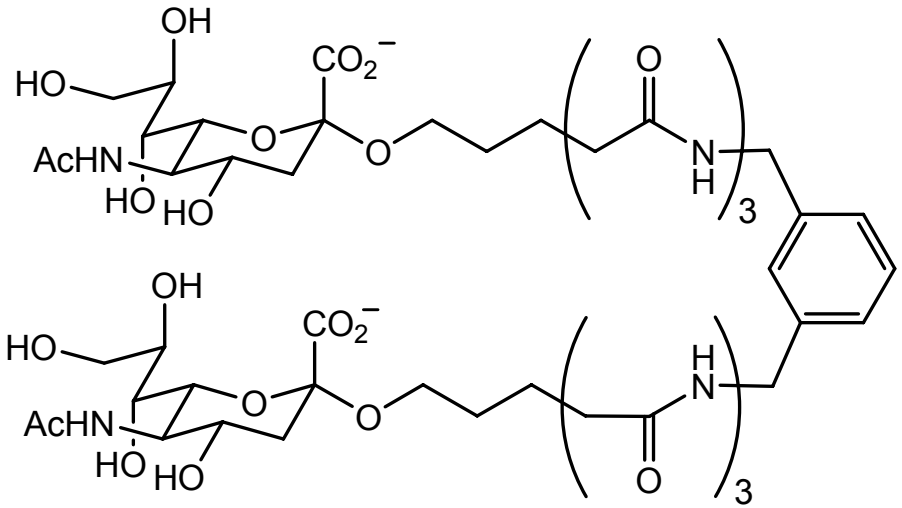
$$\beta = \frac{K_{A_2}}{K_A}$$

Just a measure of how much better a ligand A_2 is than A. (Says nothing about contribution of entropy.)



$K_{\text{sialic acid}} = 400\ M^{-1}$

β = 100



$K_{\text{sialic dimer}} = 40000\ M^{-1}$

Phenomenological Kinetics

How do we understand, predict rates of reactions from experimental data?

What do we even mean by "*rate*"? Consider:

$$N_2O_5 \longrightarrow 2\,NO_2 + \tfrac{1}{2}\,O_2$$

Could define *rate* = $\dfrac{d[N_2O_5]}{dt}$ *or* $\dfrac{d[NO_2]}{dt}$ *or* $\dfrac{d[O_2]}{dt}$

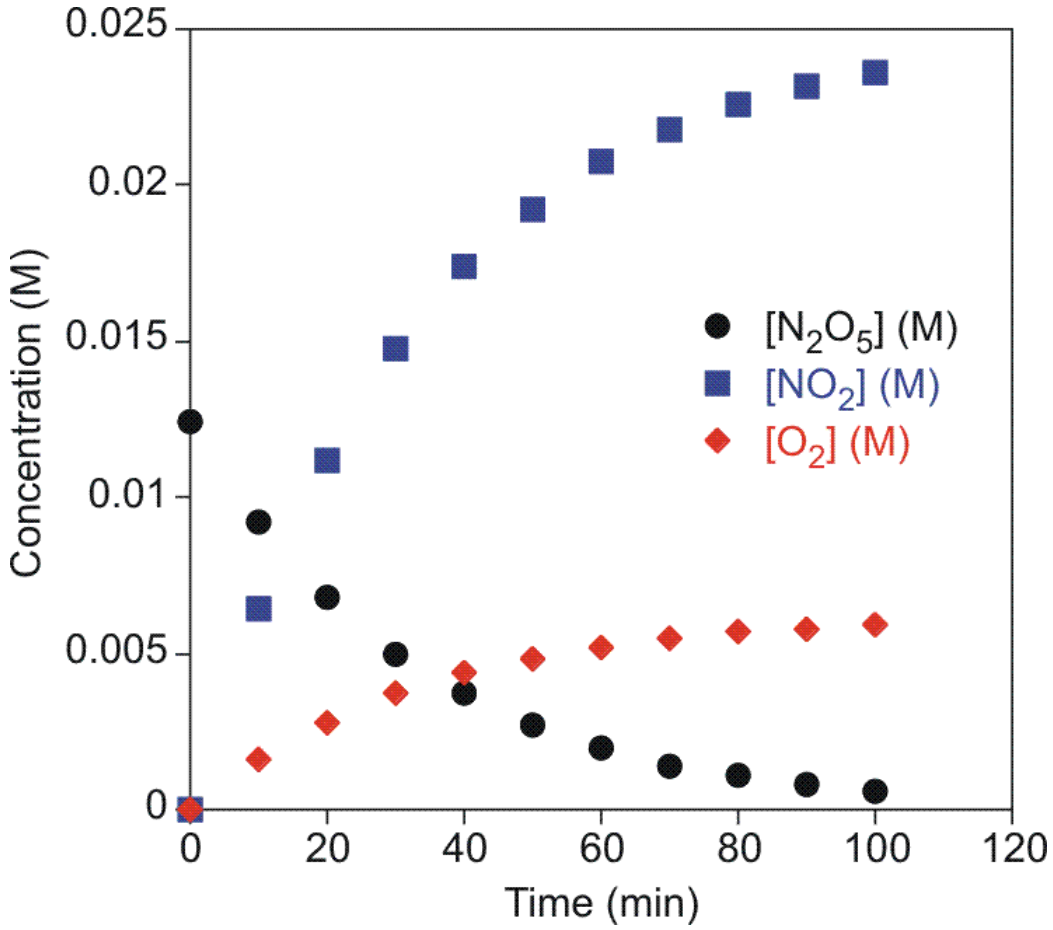
For this reaction, by definition from stoichiometry,

$$-\frac{d[N_2O_5]}{dt} = \frac{1}{2}\frac{d[NO_2]}{dt} = 2\frac{d[O_2]}{dt}$$

(For every molecule of N_2O_5 consumed, 2 of NO_2 created, etc…)

Understanding Reaction Rates

$$N_2O_5 \longrightarrow 2\,NO_2 + \tfrac{1}{2}\,O_2$$



$$-\frac{d[N_2O_5]}{dt} = \frac{1}{2}\frac{d[NO_2]}{dt}$$

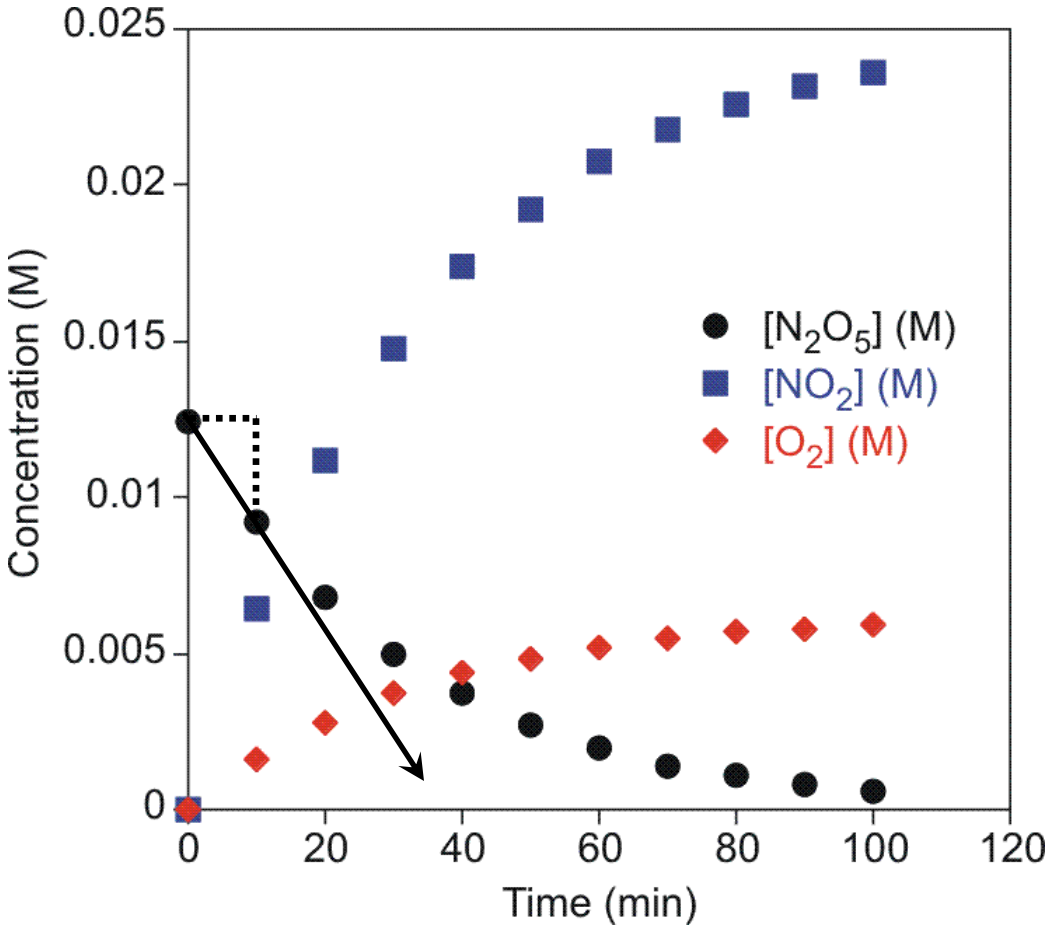
$$= 2\frac{d[O_2]}{dt}$$

True at any time.

Don't need to know anything about reaction mechanism to say this.

Measuring Reaction Rates

$$N_2O_5 \longrightarrow 2\,NO_2 + \tfrac{1}{2}\,O_2$$

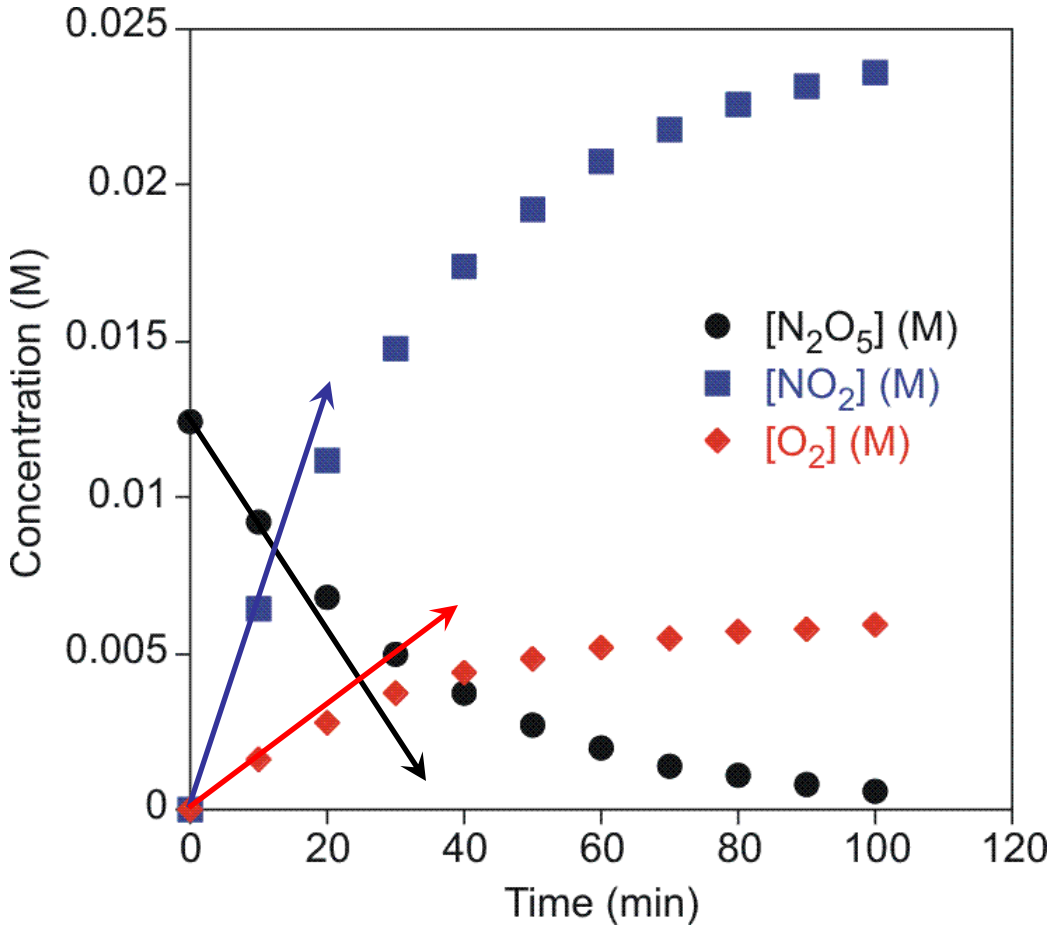


$$\frac{\Delta[N_2O_5]}{\Delta t} = \frac{(0.012\ \text{M}) - (0.009\ \text{M})}{(0\ \text{min}) - (10\ \text{min})}$$

$$= -3 \times 10^{-4}\ \text{M/min}$$

Measuring Reaction Rates

$$N_2O_5 \longrightarrow 2\,NO_2 + \tfrac{1}{2}\,O_2$$



$$\frac{\Delta[N_2O_5]}{\Delta t} = -3 \times 10^{-4}\ \text{M/min}$$

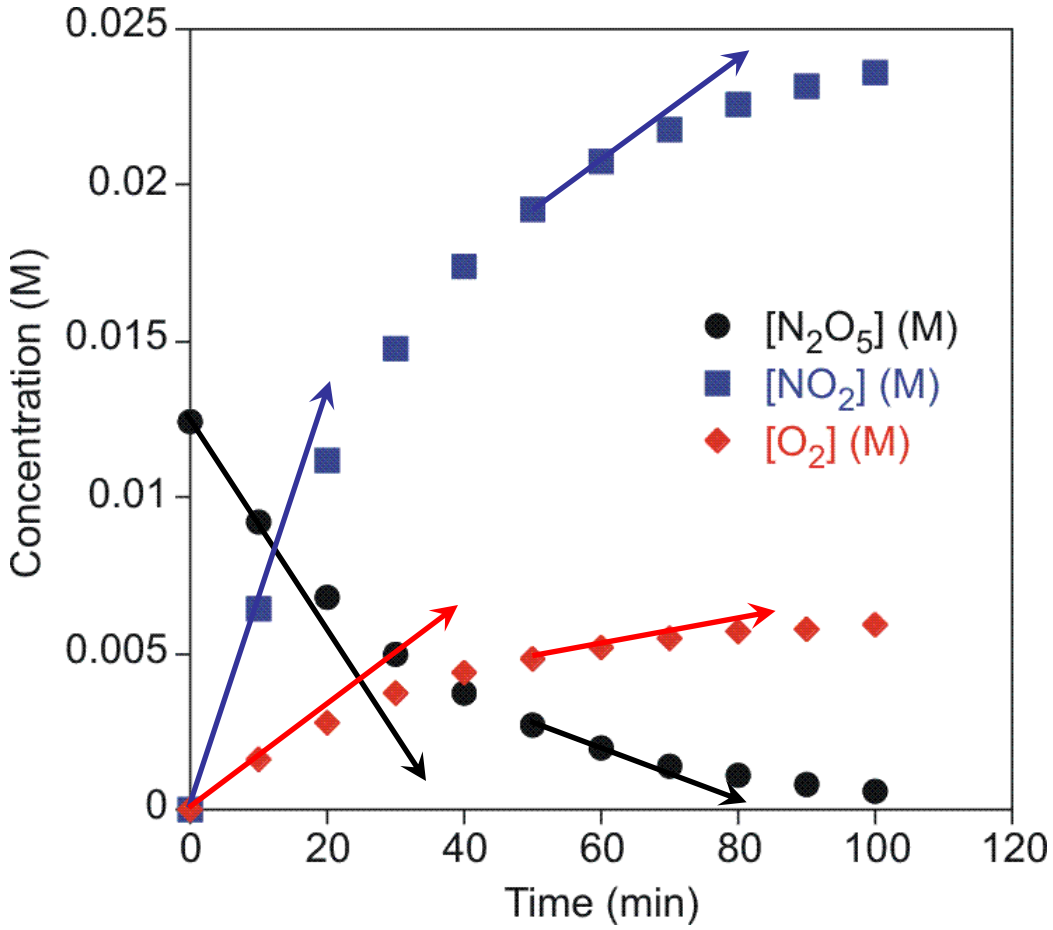
by the same method,

$$\frac{\Delta[NO_2]}{\Delta t} = 6 \times 10^{-4}\ \text{M/min}$$

$$\frac{\Delta[O_2]}{\Delta t} = 1.5 \times 10^{-4}\ \text{M/min}$$

Understanding Reaction Rates

$$N_2O_5 \longrightarrow 2\,NO_2 + \tfrac{1}{2}\,O_2$$



$$-\frac{\Delta[N_2O_5]}{\Delta t} = \frac{1}{2}\frac{\Delta[NO_2]}{\Delta t}$$

$$= 2\frac{\Delta[O_2]}{\Delta t}$$

True over any time period.

Again, don't need to know anything about reaction mechanism to say this.

Phenomenological Kinetics

Most important question:
How does rate depend on reactant concentration?

For any reaction, can write a **rate law**:

$$rate = k[\text{reagent}]^x$$

k: rate constant
x: reaction order

- *k* and *x* are determined experimentally.
- *k* = *f*(rxn, temp) and is always a positive number.
- *x* has no necessary relationship to the coefficients of the balanced chemical equation. Is usually an integer or fraction. Can be zero.

Method of Initial Rates

$$rate = k[\text{reagent}]^x$$

Problem: *rate* changes, over time, as [reagent] changes.

So, if we don't have a good way of monitoring [reagent], how do we determine *k* and *x*?

Solution: [reagent] is defined at $t = 0$, and is effectively constant at beginning of reaction (first few %)

So measure multiple rates at $t = 0$ for different starting concentrations [reagent], solve for *k* and *x*.

Method of Initial Rates

Consider: $2\ NO + Br_2 \longrightarrow 2\ NOBr$

For $rate = k[NO]^x[Br_2]^y$, what are k, x, y?

Solution: Vary each concentration independently; solve for variables.

Run #	$[NO]_0$ (M)	$[Br_2]_0$ (M)	$\{d[Br_2]/dt\}_0$ (M/min)
1	1.00	1.00	1.3×10^{-3}
2	1.50	1.00	2.93×10^{-3}
3	1.50	3.00	8.78×10^{-3}

(answer on the board)

Consider: $2\ NO + Br_2 \longrightarrow 2\ NOBr$

For $rate = k[NO]^x[Br_2]^y$, what are k, x, y?

Solution: Vary each concentration independently; solve for variables.

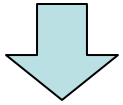
Run #	$[NO]_0$ (M)	$[Br_2]_0$ (M)	$\{d[Br_2]/dt\}_0$ (M/min)
1	1.00	1.00	1.3×10^{-3}
2	1.50	1.00	2.93×10^{-3}
3	1.50	3.00	8.78×10^{-3}

Method of Initial Rates

$$d[Br_2]/dt = k[NO]^x[Br_2]^y$$

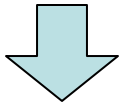
$$d[Br_2]/dt_{(run\ 1)} = k[NO]_{(run\ 1)}^x[Br_2]_{(run\ 1)}^y$$

$$d[Br_2]/dt_{(run\ 2)} = k[NO]_{(run\ 2)}^x[Br_2]_{(run\ 2)}^y$$



$$\frac{d[Br_2]/dt_{(run\ 1)}}{d[Br_2]/dt_{(run\ 2)}} = \frac{k[NO]_{(run\ 1)}^x[Br_2]_{(run\ 1)}^y}{k[NO]_{(run\ 2)}^x[Br_2]_{(run\ 2)}^y}$$

For runs 1 and 2, we made $[Br_2]$ the same. $[Br_2]_{(run\ 1)}^y = [Br_2]_{(run\ 2)}^y$.



Method of Initial Rates

$$\frac{d[Br_2]/dt_{(run\ 1)}}{d[Br_2]/dt_{(run\ 2)}} = \frac{[NO]_{(run\ 1)}{}^{x}}{[NO]_{(run\ 2)}{}^{x}}$$

$$\frac{1.3 \times 10^{-3}\ M/min}{2.93 \times 10^{-3}\ M/min} = \frac{(1.00\ M)^{x}}{(1.50\ M)^{x}} = \left(\frac{1.00\ M}{1.50\ M}\right)^{x}$$

Solution: $x = 2$.

Using the same method for runs 2 and 3,
$([NO]_{(run\ 2)}{}^{x} = [NO]_{(run\ 3)}{}^{x})$,
$y = 1$;

Plug these x and y into any relation, get
$k = 1.3 \times 10^{-3}\ M^{-2}min^{-1}$.

Method of Initial Rates

Pros: Decomposition or other subsequent reactions play no role in initial rate, so data very reliable.

Good for enzyme, polymerization kinetics.

Cons: Have to perform multiple reaction runs; each run contributes only one data point.

Must start data acquisition at $t = 0$, the only time concentrations are known.

There is a better way: integrated rate laws.