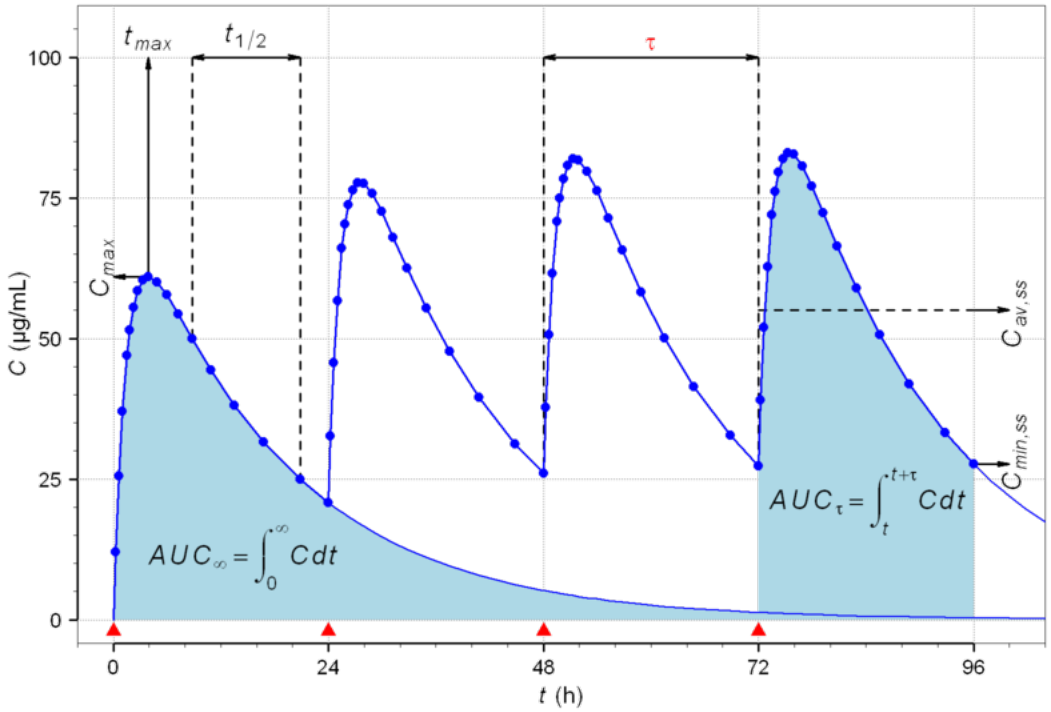
Drug Kinetics. Rate Laws

Real kinetics, Zero and First Order, Examples



The time course of drug plasma concentrations over 96 hours following oral administrations every 24 hours

Integrated Rate Laws

Integrated Rate Laws give the concentrations of reactants and products as function of time

Zero-order reactions do NOT depend on the concentration and are limited by an external (constant) concentration of factor.

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -k_0, \qquad k_0 = \left[\mathrm{mol\ L^{-1}\ s^{-1}}\right]$$

Zero-order Integrated Rate Law

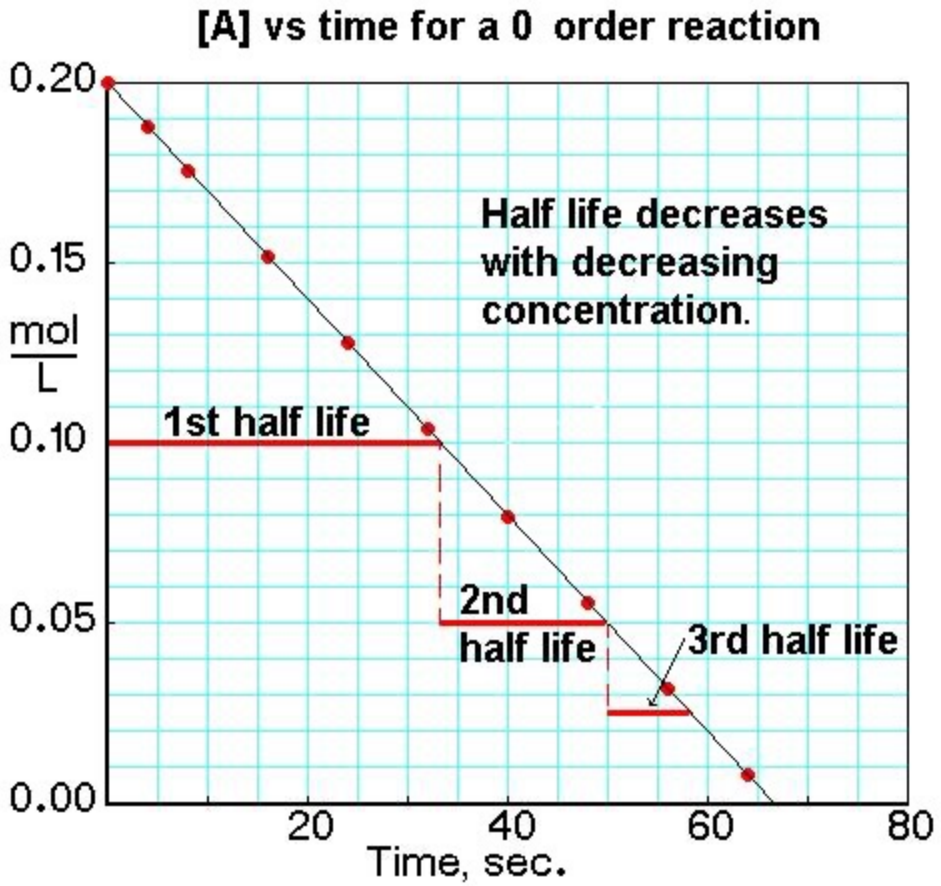
$$[\mathrm{A}] = [\mathrm{A}]_\mathrm{o} - k_0 t$$

Half-life of the Zero-Order Reaction

- $t_{½} = A_0 / 2k_0$

- Examples:
  - Degradation of suspensions or solid state
  - Dissolution of drug crystals (assuming infinite dilution)

- Pseudo-zero-order: an elimination bottleneck



First Order reaction

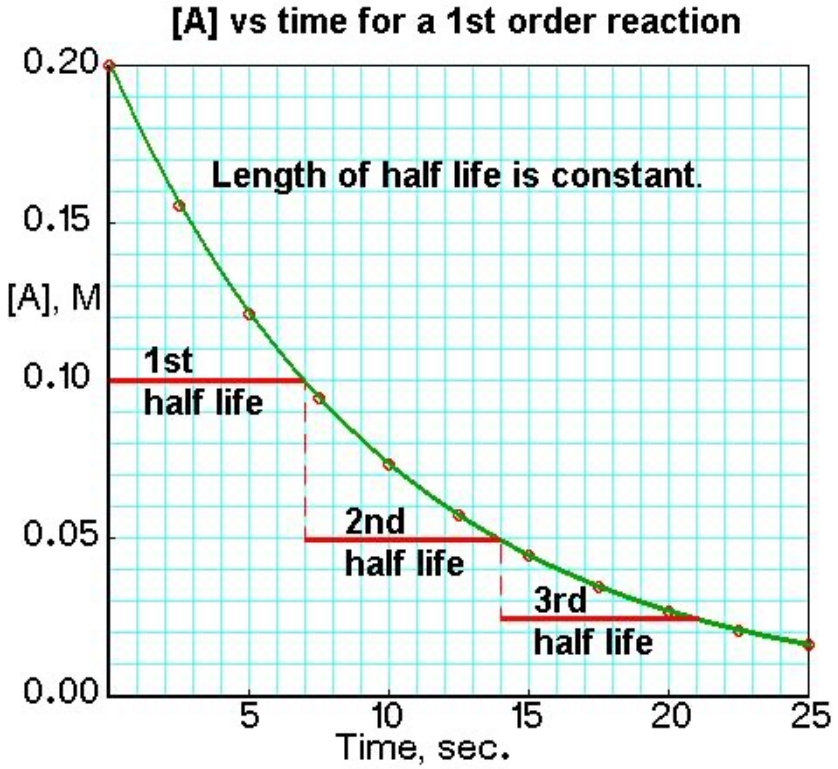
- The ***rate*** is proportional to the concentration.
- Example, radioactive decay:

$$\frac{\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = -k[\mathrm{A}], \qquad k = \left[\mathrm{s}^{-1}\right]$$

- ***k*** is ***rate constant***
- 1st order ***Integrated Rate Law***:

$$[\mathrm{A}] = [\mathrm{A}]_\mathrm{o}\,\mathrm{e}^{-kt}$$

- ***Half-life does not depend on C_0***

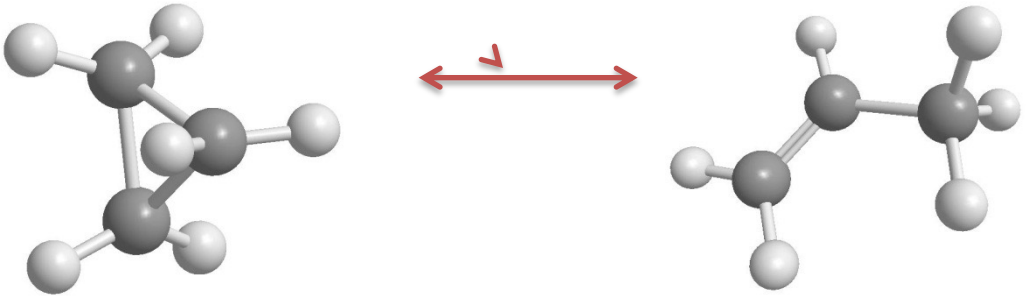


$$\frac{1}{2}[\mathrm{A}]_\mathrm{o} = [\mathrm{A}]_\mathrm{o}\,\mathrm{e}^{-kt_{1/2}} \Rightarrow \frac{1}{2} = \mathrm{e}^{-kt_{1/2}} \Rightarrow \frac{1}{2} = \mathrm{e}^{-kt_{1/2}} \Rightarrow kt_{1/2} = \ln 2$$

$$t_{½} = \ln 2 / k = 0.693 / k$$

Uni-molecular Reactions

First order (e.g. A ↔ B) reaction. Initially: ***Rate = k [A]***

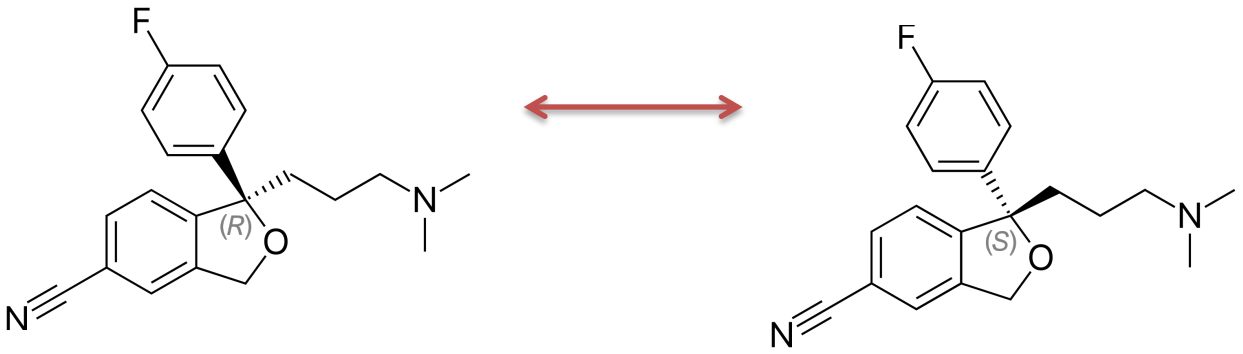


Cyclopropane

Propene

Citalopram R

Citalopram S



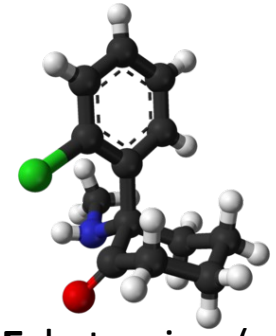
Racemic and Enantiopure drugs

Racemic mixture	Single-enantiomer (**entantiopure**)
Amlodipine (Norvasc)	Levamlodipine (EsCordi Cor)
Amphetamine (Benzedrine)	Dextroamphetamine (Dexedrine)
Bupivacaine (Marcain)	Levobupivacaine (Chirocaine)
Cetirizine (Zyrtec / Reactine)	Levocetirizine (Xyzal)
Chlorphenamine (INN)	Dexchlorpheniramine (Polaramine)
Citalopram (Celexa / Cipramil)	Escitalopram (Lexapro / Cipralex)
Fenfluramine (Pondimin)	Dexfenfluramine (Redux)
Formoterol (Foradil)	Arformoterol (Brovana)
Ibuprofen (Advil / Motrin)	Dexibuprofen (Seractil)
Ketamine (Ketalar)	Esketamine (Ketanest S)
Ketoprofen (Actron)	Dexketoprofen (Keral)
Methylphenidate (Ritalin)	Dexmethylphenidate (Focalin)
Milnacipran (Ixel / Savella)	Levomilnacipran (Fetzima)
Modafinil (Provigil)	Armodafinil (Nuvigil)
Ofloxacin (Floxin)	Levofloxacin (Levaquin)
Omeprazole (Prilosec)	Esomeprazole (Nexium)
Salbutamol (Ventolin)	Levalbuterol (Xopenex)
Zopiclone (Imovane / Zimovane)	Eszopiclone (Lunesta)

Prefixes:
(**S**): Leva, Levo, Es, Sinistra, (left)

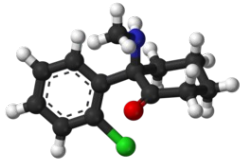
(**R**): Dextro, Dex, Ar, (right)

Example:

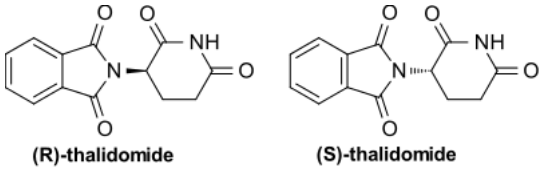


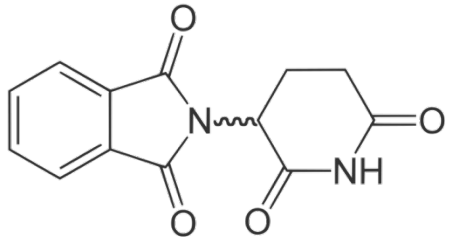
Esketamine (ok)

Arketamine (☹)

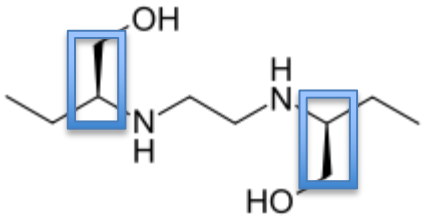


The *Timing* of Dangerous transitions



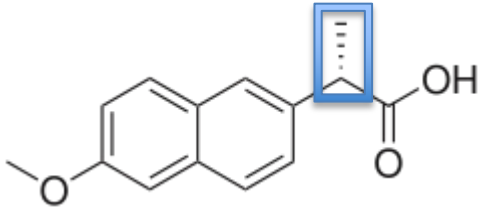


Thalidomide: One enantiomer is effective against morning sickness, whereas the other is teratogenic. However, the enantiomers are converted into each other in vivo. Dosing with a single-enantiomer form of the drug will still lead to both the D and L isomers eventually being present in the patient's serum and thus would not prevent side effects (though it might reduce them if the rate of in vivo conversion can be slowed).



Ethambutol: Whereas one enantiomer (S,S) is used to treat *tuberculosis*, the other (R,R) causes *blindness*.

Naproxen: (S)-(+)-naproxen is used to treat arthritis pain, but (R)-(–)-naproxen causes *liver poisoning* with no analgesic effect.

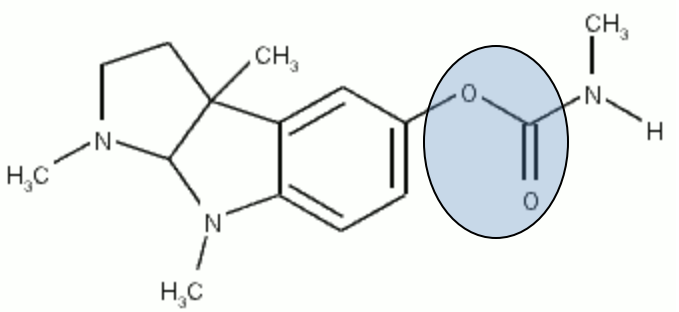


The Chemical Decomposition: Hydrolysis

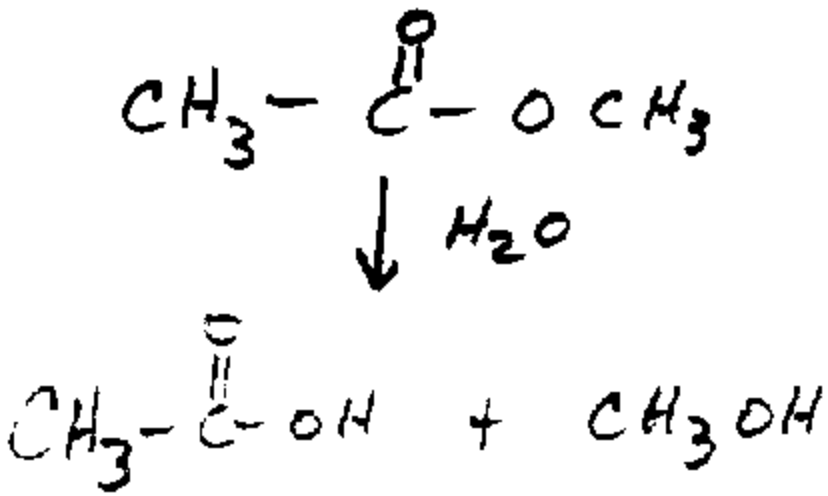
- If *half life* is *independent on the initial concentration*, i.e. **hydrolysis,** it is the first order reaction
- **Pseudo-first order kinetics**: one of the reactants is in large excess
- Liquid dosage form + drug decomposition in vivo

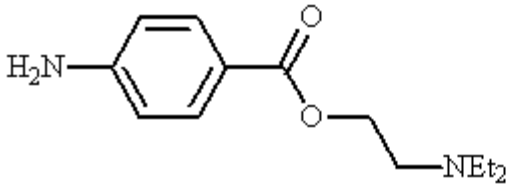
Hydrolysis: Ester

- R-**C(=O)O**-R’
- Methyldopate, tetracaine, procaine, etc.
- Faster at acidic pH



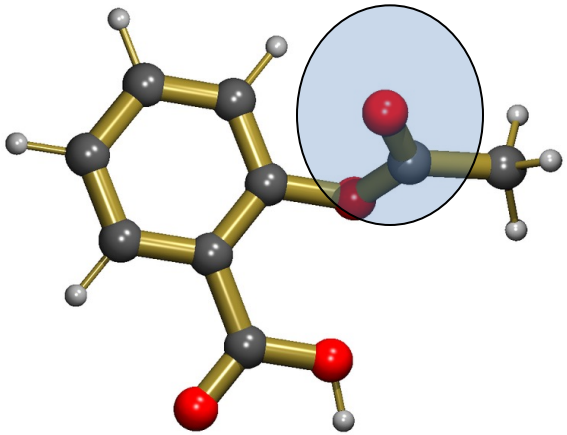
Physostigmine (cholinesterase inhibitor) is used to treat glaucoma and delayed gastric emptying



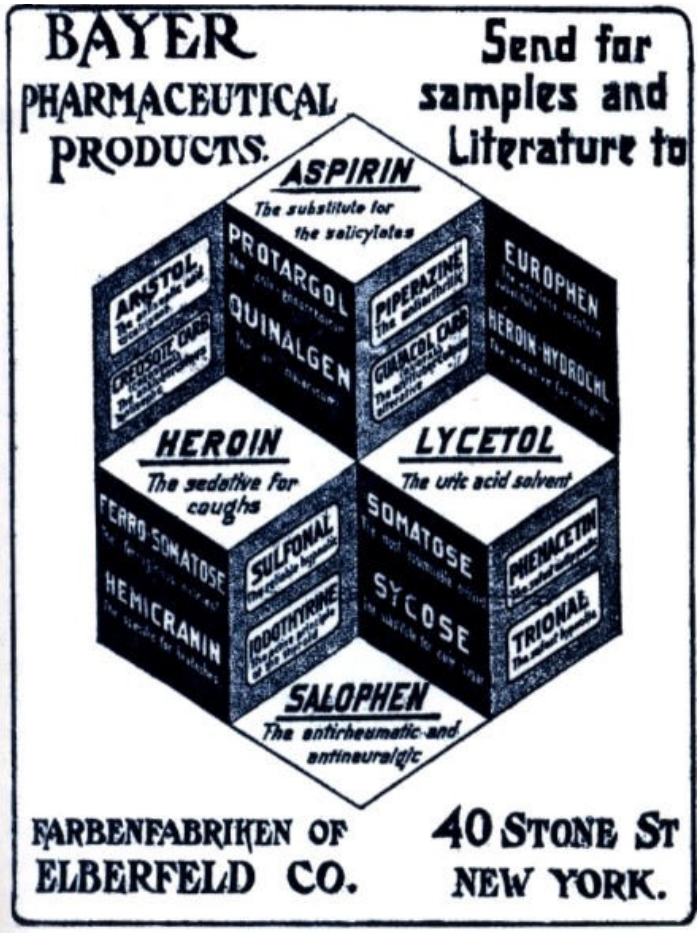


Procaine

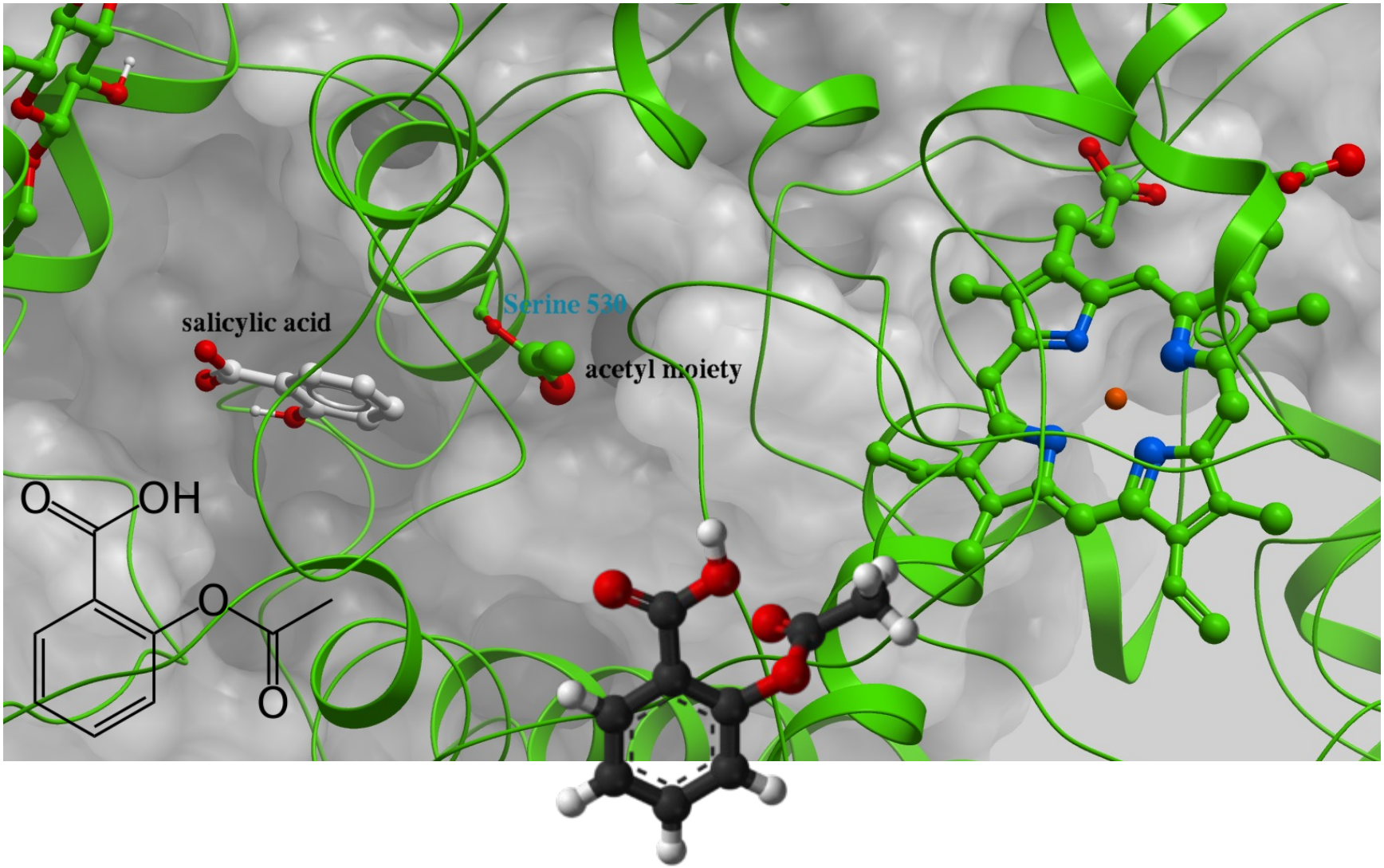
Timing of Ester Hydrolysis of Aspirin in solution



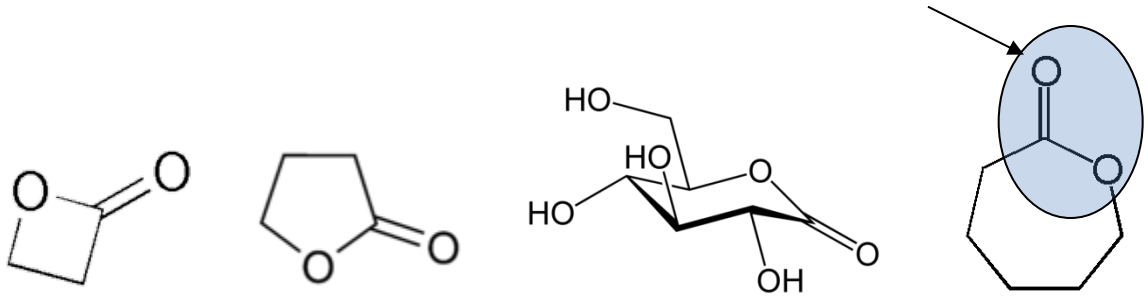
- Invented by Felix Hoffman, patented by Bayer in 1899
- Cleavage of the Aspirin ester is a part of its COX-1/2 inactivation mechanism
- 1% a day hydrolysis of suspension of aspirin



Aspirin Acetylates Serine 530 in Cox2



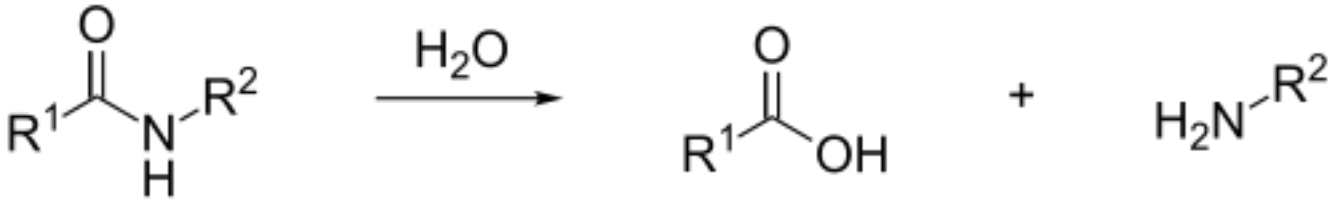
Hydrolysis: Lactones, Amide



β-propiolactone γ-butyrolactone (GBL) glucono delta-lactone (GDL) Caprolactone

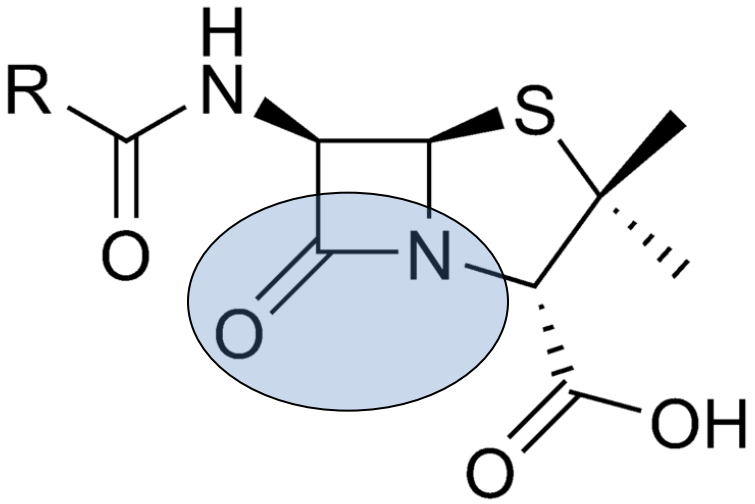
- A **cyclic ester**
- Lactones are hydrolyzed

- **Amide:** R-**C(=O)N**H_2
- The reaction is catalyzed by either acid or base

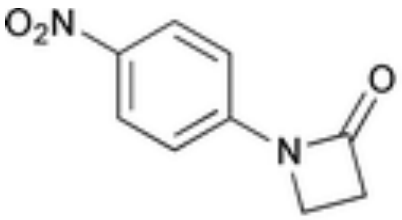


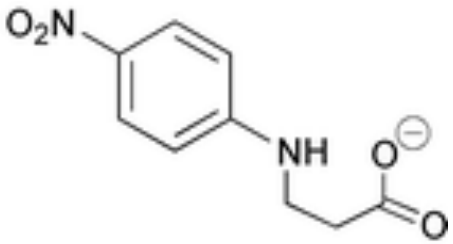
Hydrolysis: Lactam

- A **cyclic amide**.
- Beta-lactam antibiotics

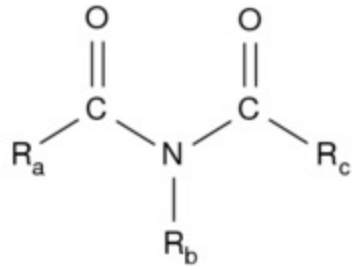


Penicillin-core

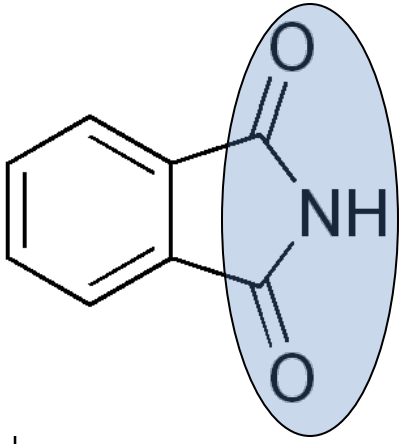


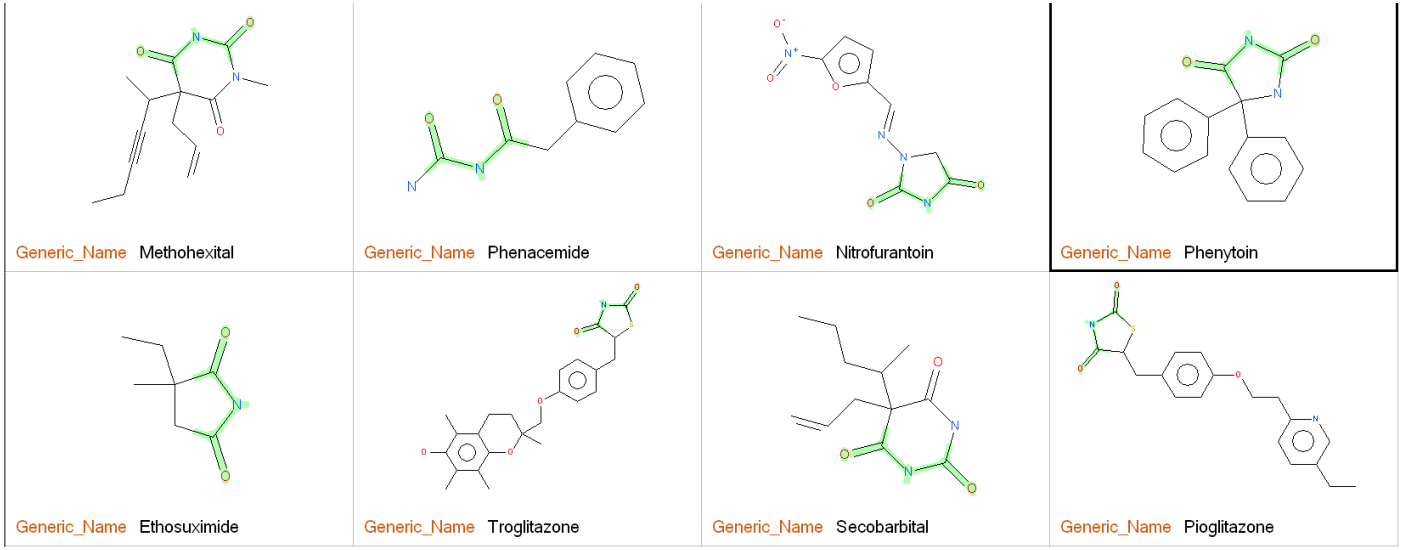


Hydrolysis: Imide



- R-**C(=O) NH C(=O)-**R’
- Some imide-containing drugs

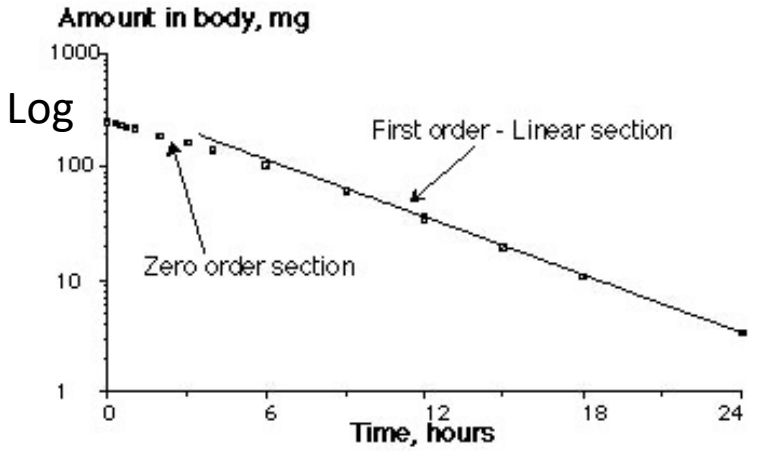




1st Order : Log**C** vs **t** plot: **t** ½ and **k**

For exponential decay $C = C_o e^{-kt}$, $\ln(C/C_0) = -kt$

- Plot **Log_{10}(Amount)** vs **time**
- If it is a *straight line*, the reaction follows the **1st order kinetics**
- Calculate the slope
- k_1 = Slope/ln10 = Slope/2.3
- $t_{½} = 0.69/k_1$

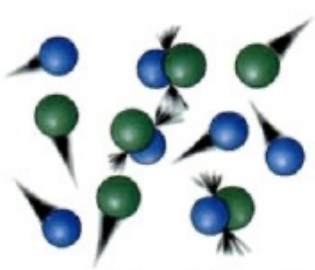


Example problem: 1st order reaction

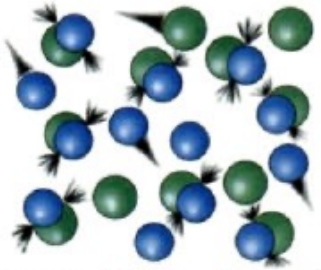
- **Q:** Thalidomide undergoes spontaneous conversion from (+) form to (-) form and vice-versa, with the rate of conversion depending on the composition of the solution. For example, the half-life of (+)Thalidomide in human plasma is 11.5 minutes. Estimate the ***rate constant*** for the reaction of conversion of (+)Thalidomide into (-)Thalidomide in human plasma.
- **Hints:**
  - Enantiomer conversion is 1st order; hence constant $t_{1/2}$
  - Asks for **rate constant** (k), not **rate** ($d[A]/dt = -k[A]$)
- **S:** use $kt_{1/2} = \ln 2$. $t_{1/2} = 11.5$ min = 690 s. The rate constant is $k = \ln 2 / t_{1/2} = \ln 2 / 690 \sim 0.001\ s^{-1}$
- **A:** 0.001 s^{-1}

Second Order reactions

- Rate is determined by the concentrations of two reacting species



Low concentration = Few collisions



High concentration = More collisions

$$\frac{d[A]}{dt} = -k_2[A][B], \quad k = \left[M^{-1}s^{-1}\right]$$

- If both initial concentrations are the same, or both components are the same reactant

$$\frac{d[A]}{dt} = -k[A]^2, \quad k = \left[M^{-1}s^{-1}\right]$$

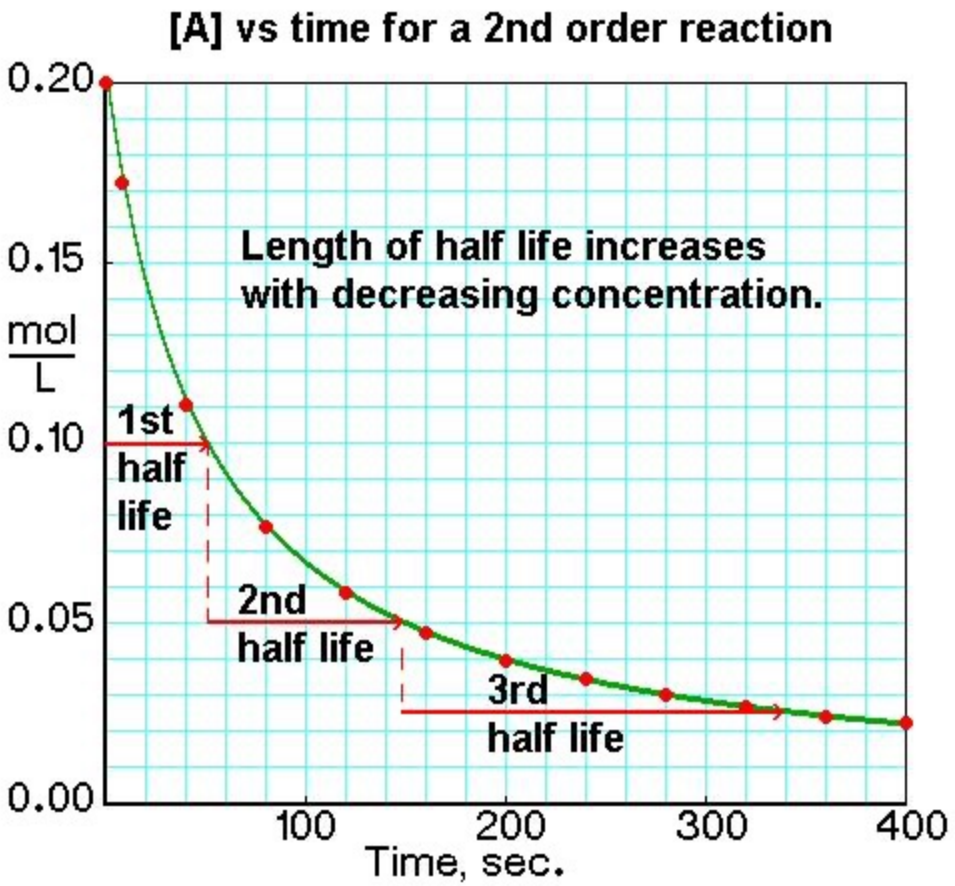
Second order

- A+B to products
- 2A to products
- E.g. [P]+[L] $\leftrightarrow$ [PL] (in 1:1 stoichiometry)
- Integrate Rate Law:

$$\frac{1}{[A]} - \frac{1}{[A]_0} = k_2 t$$

- Half life (changing):

$$t_{1/2} = \frac{1}{k_2 [A]_0}$$

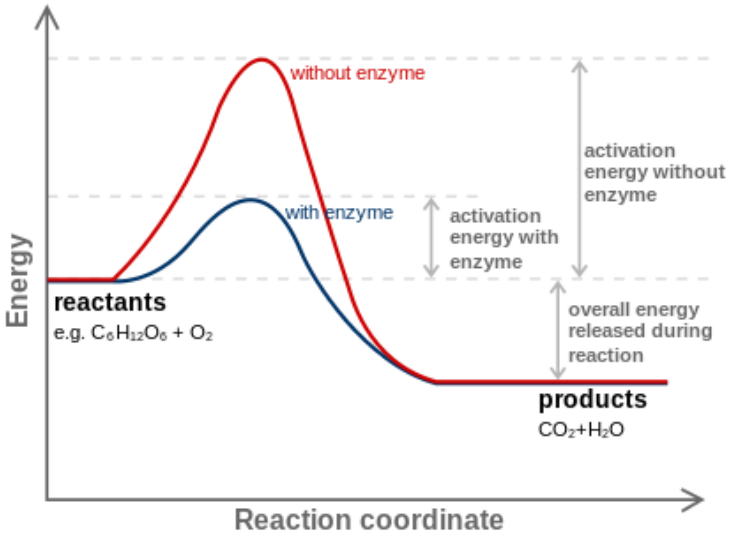


Example problem: 2nd order reaction

- **Q:** The 1:1 binding reaction between a drug and its protein target is first order with respect to each of the reactants. In the solution of 1 nM protein and 100 nM drug, the ***initial rate*** of complex formation was found to be 12 pM/s. What will be the initial rate of complex formation in the solution of 1 μM protein and 1 μM drug?
- **Hints:**
  - ***First order*** in ***each of the reactants*** means that d[PD]/dt = k[P][D]. The reaction is 2nd order altogether.
  - Asks for **rate** ($d[PD]/dt$)

- **S:** When [P] is increased from 1 nM to 1 μM (1000-fold increase), and [D] is increased from 100 nM to 1 μM (10-fold increase), the rate must increase 10000-fold. The new rate will then be 12 pM/s x 10^4 = 120 nM/s.
- **A:** 120 nM/s

Arrhenius equation



- The **rate constant** of chemical reaction, k

$$k = (Pf)e^{-\frac{G_{activation}}{RT}}$$

Pf is the pre-exponential factor (pre-factor)

Svante Arrhenius, Swedish physical chemist. In 1903 he became the first Swede to be awarded the Nobel Prize in chemistry.

Thermodynamics equilibrium

$$K = e^{-\frac{G_{AB}}{RT}}$$

Jacobus van't Hoff