



# Free-Radicals: Chemistry and Biology

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<http://iscamap.chem.polimi.it/citterio/education/free-radical-chemistry/>



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# Free Radical Kinetics

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## Acronyms used in Kinetics

- **Common symbols**

$k$  rate constant (*n.b. lower case*)

$K$  equilibrium constant (upper case)

$[X]$  concentration of species X

$t_{1/2}$  half-life

$\tau$  lifetime of excited state =  $1 / k$

- Linking **rate constants** to reaction numbers

$k_n$  rate constant of reaction (n)

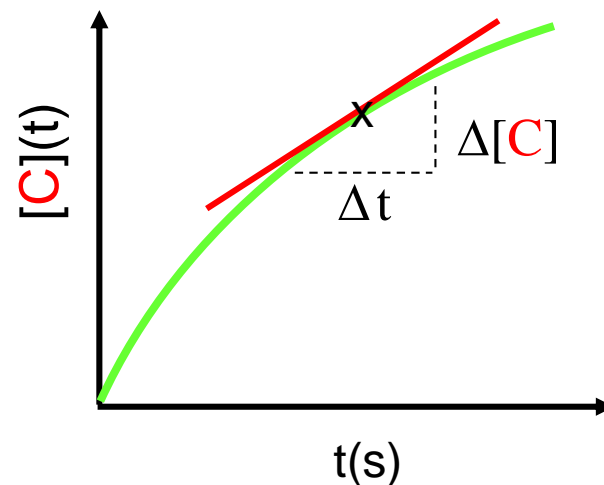
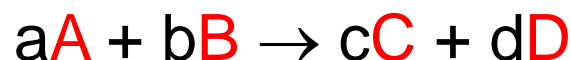
$k_{-n}$  rate constant of reverse reaction  
of equilibrium (n)

$k_f$  ( $k_r$ ) rate constant of forward (reverse)  
reaction of equilibrium



# Rate of Reaction

- Definition: **Rate** of a reaction is the rate of change of amount (formation) of a product, or rate of loss of a reactant
  - units: concentration (molar if in solution) per unit time.
- For work at constant volume, can use intensive units such as rate of change of concentration ( $\text{mol dm}^{-3}\text{s}^{-1}$ ) or partial pressure ( $\text{bar s}^{-1}$ )
- Can define rate in terms of any reactant or product but need to adjust for the stoichiometry



$$r = \lim_{\Delta t \rightarrow 0} \frac{\Delta c}{\Delta t}$$

$$\text{rate } r = -\frac{1}{a} \frac{dC_A}{dt} = -\frac{1}{b} \frac{dC_B}{dt} = +\frac{1}{c} \frac{dC_C}{dt} = +\frac{1}{d} \frac{dC_D}{dt}$$



## Reaction Rate Laws and Reaction Order

- Reaction rates usually depend on the concentrations or pressures of the reactants.
- Consider the reaction  $A + 2 B \rightarrow C + 2D$
- The empirical reaction law may be found by experiment to be

$$\text{rate } r_a = -\frac{dC_A}{dt} = k \cdot C_A^a \cdot C_B^b$$

- $k$  is the reaction rate constant. Units depend on the overall reaction order.
- The reaction is of order  $a$  with respect to reactant  $A$  and order  $b$  with respect to reactant  $B$ . If  $a = 1$  or  $2$  then we say 1<sup>st</sup> order or 2<sup>nd</sup> order with respect to  $a$
- The overall **reaction order** is  $a + b$ .
- Reaction order is a convenient classification. Values can be negative. They are often not whole numbers (non-integral). Products can be involved as well.



## Rate Constants (Coefficients) are the Key

- The **rate** of a reaction is often proportional to concentration (denoted by square brackets)
  - $A \rightarrow \text{product(s)}$ 
    - rate of loss of  $A \propto [A]$   
 $= k [A]$
  - $A + A \rightarrow \text{product(s)}$ 
    - rate of loss of  $A \propto [A]^2$   
 $= 2k [A]^2$  (n.b.  $k$  or  $2k$ ?)
  - $A + B \rightarrow \text{product(s)}$ 
    - rate of loss of  $A$  ( $B$ )  $\propto [A] [B]$   
 $= k [A] [B]$
- The **rate constant**  $k$  quantifies this proportionality
  - the larger the value of  $k$ , the higher the reactivity



## Rate is not the Same as Rate Constant

- **Rate** of a reaction is the rate of formation of a product, or rate of loss of a reactant
  - units: concentration (molar if in solution) per unit time
- **Rate constant** ( $k$ , not  $K$ ) characterizes reactivity rather than the rate under specific conditions
  - units vary with reaction type
    - $s^{-1}$  for unimolecular decay
    - $M^{-1}\cdot s^{-1}$  ( $dm^3\cdot mol^{-1}\cdot s^{-1}$ ) for bimolecular reactions
- Even (especially?) experts often wrongly use '**rate**' when they should use '**rate constant**'
  - reactions with high rate constants are not always fast.





## Rate Constants: which is the upper limit?

- Rate constants can span many **orders of magnitude**, so the **exponent** is most important:
  - $k(\text{O}_2^{\cdot-} + \text{ascorbate}) = 5.0 \times 10^4 \text{ M}^{-1}\cdot\text{s}^{-1}$
  - $k(\text{O}_2^{\cdot-} + \text{nitric oxide}) \approx (3.8 - 15) \times 10^9 \text{ M}^{-1}\cdot\text{s}^{-1}$
- **Upper limit:** reactions limited only by diffusion of species (related to viscosity  $\eta$ ,  $k_{\text{diff}} \approx 8 RT / (3 \eta)$ )
  - $k_{\text{diff}}$  for reaction in water  $\sim 7 \times 10^9$  to  $3 \times 10^{10} \text{ M}^{-1}\cdot\text{s}^{-1}$
- Most experimental values at **room temperature**
  - $k$  for electron transfer from nitroarene radical anion to oxygen increases  $\sim 2$ -fold between  $25^\circ\text{C}$  and  $37^\circ\text{C}$



## Diffusion Coefficients for Small Molecules

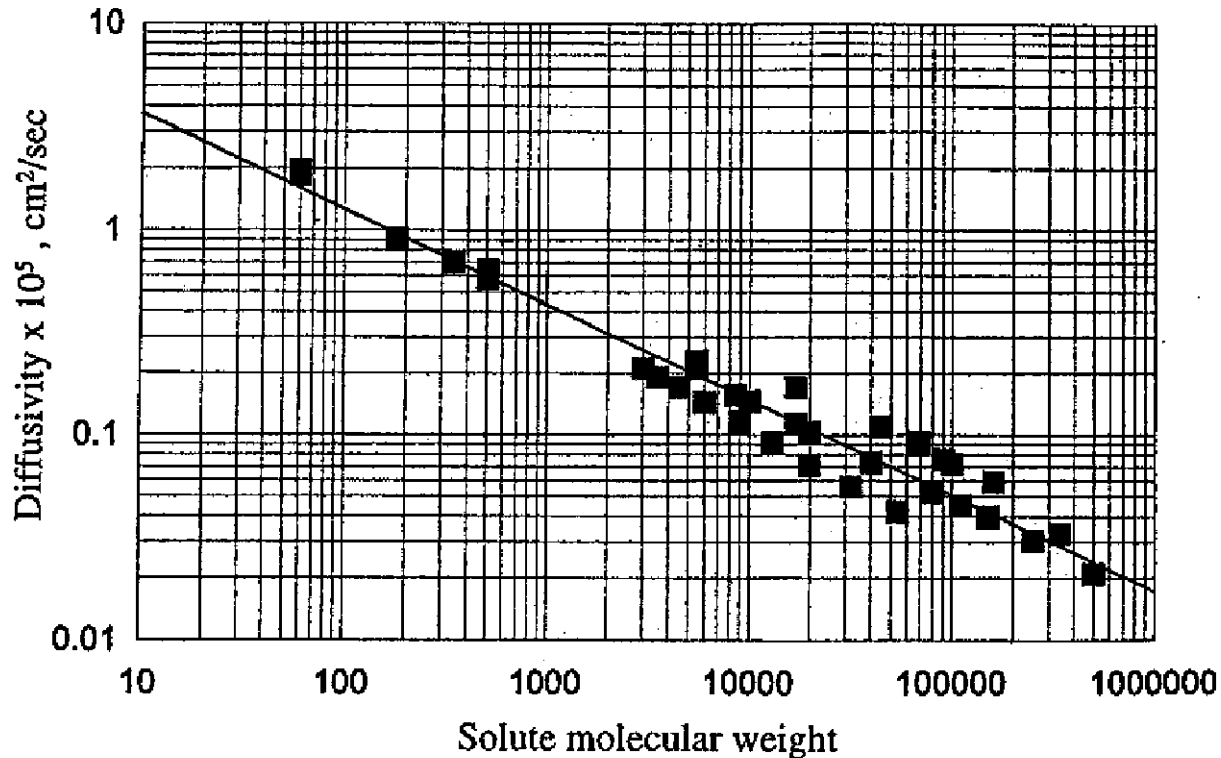
- In water at 25°C (about 25% higher at 37°C) diffusivity

<b>Solute</b>	<b><math>D / 10^{-9} m^2 s^{-1}</math></b>	<b>MW</b>
NO <sup>•</sup>	3.3	~30
O <sub>2</sub>	2.4	32
CO <sub>2</sub>	1.9	44
NO <sub>2</sub> <sup>•</sup>	1.4	46
ethanol	1.2	46
glycine	1.1	75
glucose	0.7	180
sucrose	0.5	342

- Viscosity of blood plasma ~ 1.6 × that of water
- Viscosity of cytosol may be ~ 1.2 – 4 × water



# Diffusion Coefficients for Large Molecules



Haemoglobin  
(~68 kDa):

$$D \sim 7 \times 10^{-11} \text{ m}^2 \cdot \text{s}^{-1}$$

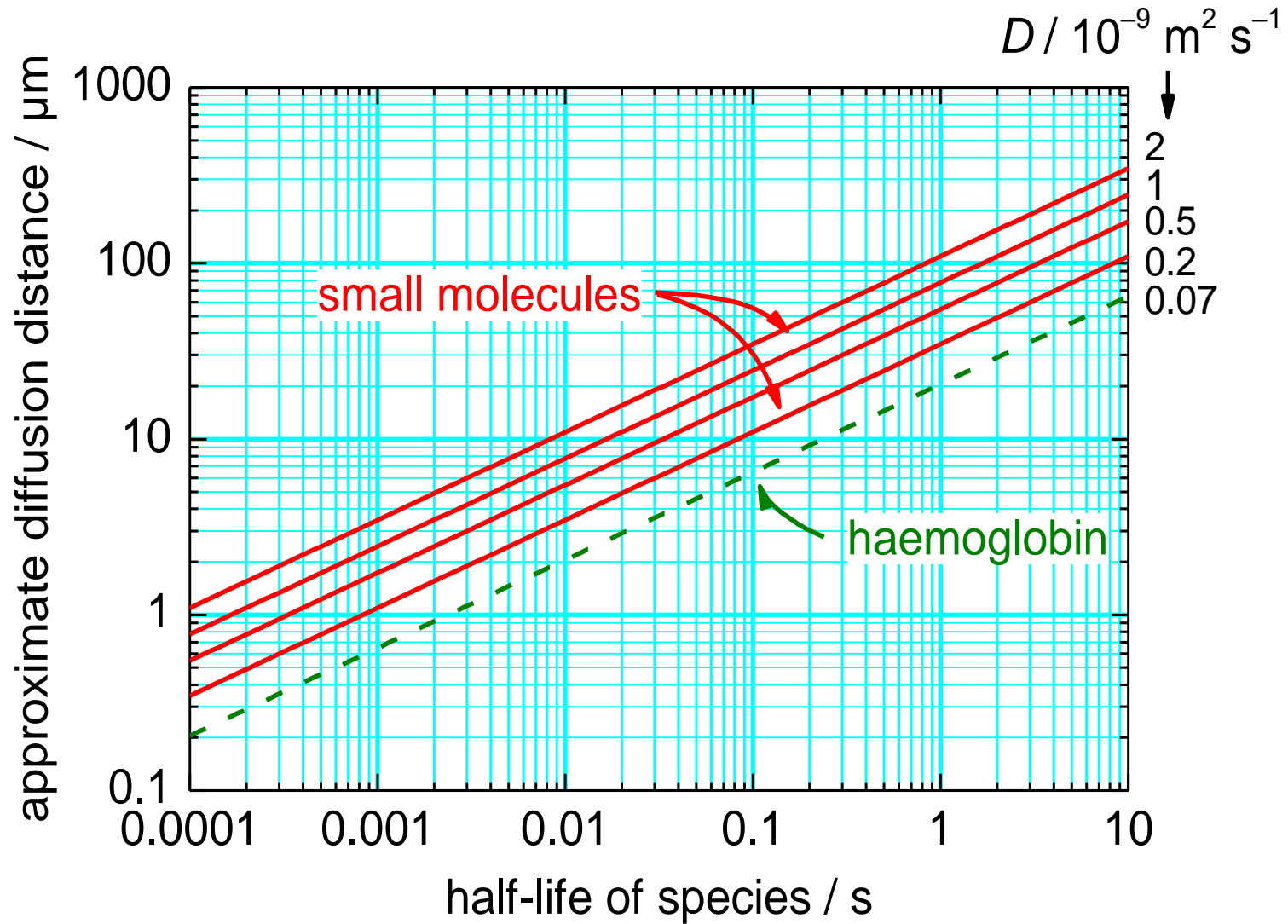
$$D \approx 1.0 \times 10^{-8} M^{-0.46} \text{ m}^2 \cdot \text{s}^{-1} \text{ (water, 37}^\circ\text{C)}$$

where  $M$  is the molecular weight

Fournier, R. L., 1999, *Basic Transport Phenomena in Biomedical Engineering* (Taylor & Francis, Philadelphia)

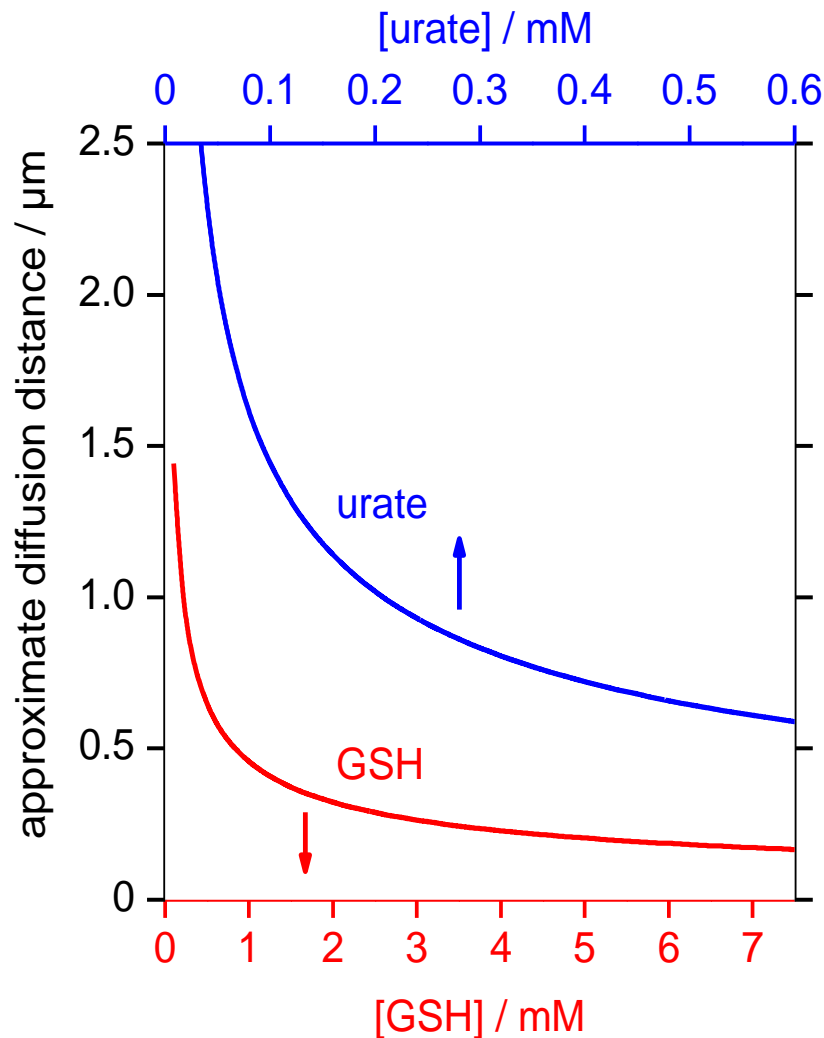


# Approximate Diffusion Distances





## Diffusion of a Highly-Reactive Radical: $\text{NO}_2^\cdot$



- $D \sim 1 \times 10^{-9} \text{ m}^2 \cdot \text{s}^{-1}$
- $k \sim 2 \times 10^7 \text{ M}^{-1} \cdot \text{s}^{-1}$  for both GSH and urate at pH  $\sim 7.4$ 
  - If [GSH]  $\sim 5 \text{ mM}$ ,  
 $x \sim 0.2 \text{ } \mu\text{m}$
  - If [urate]  $\sim 0.3 \text{ mM}$ ,  
 $x \sim 0.8 \text{ } \mu\text{m}$
- All reactants define  $t_{1/2}$ 
  - $t_{1/2} \sim 0.7 / \Sigma(k[\text{scavenger}])$



# Temperature Dependence of Rate Constant: Arrhenius Law

$$k = A \exp\left(\frac{-E_a}{RT}\right)$$

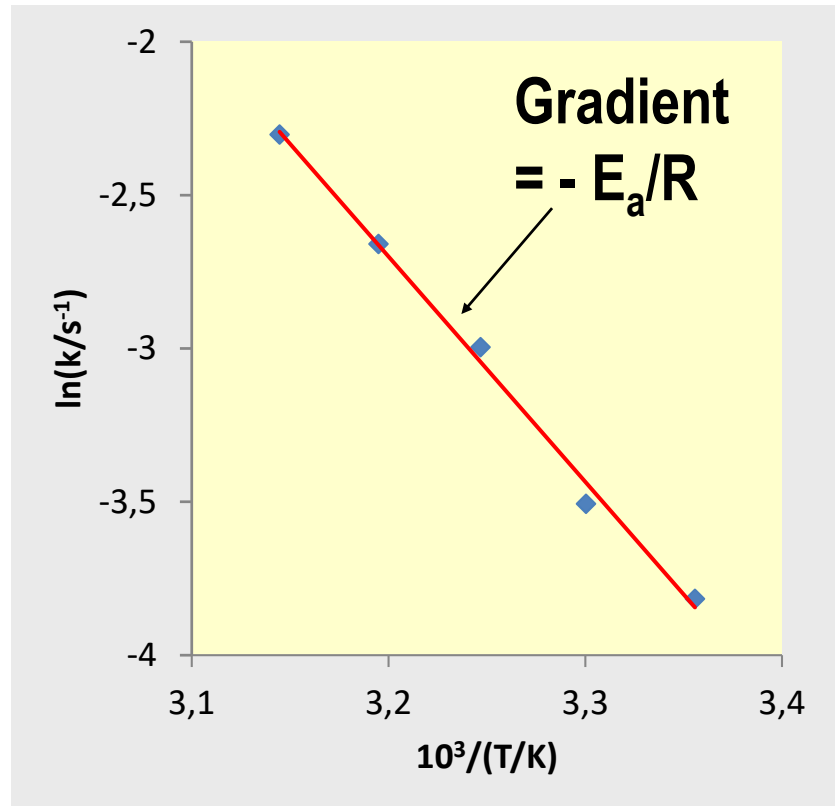
Hence

$$\ln k = \ln A - \frac{E_a}{RT}$$

A = pre-exponential factor

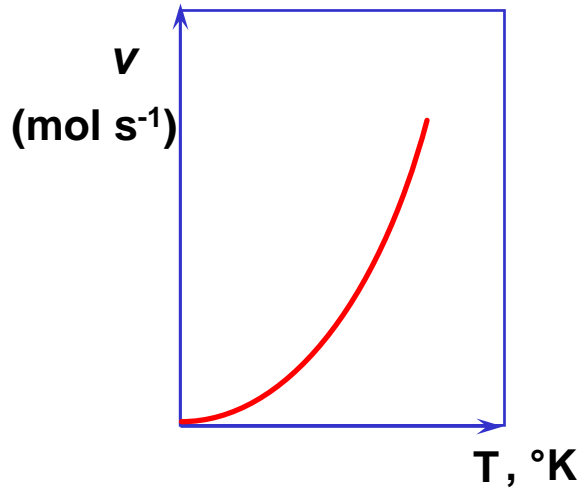
E = activation energy /

T = absolute temperature / K



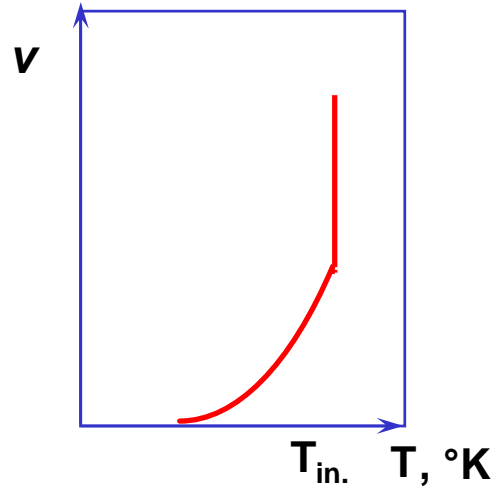


# Temperature Dependence of Reaction Rates



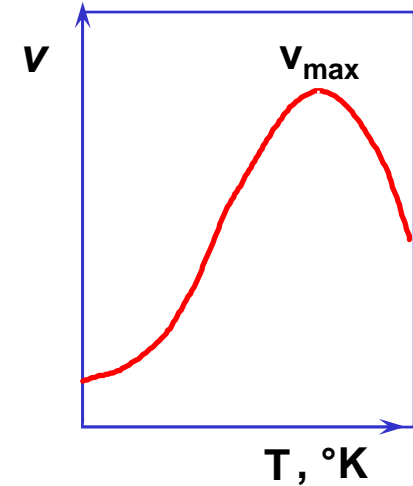
***Kinetic of typical reaction (Arrhenius law)***

The rate increases 2-3 times for a  $10^{\circ}\text{C}$  increase in temp..



***Kinetic of explosive reaction***  
( $T_{in.}$  = initiation temp.)

The rate increases normally until  $T_{in.}$ , then grows drastically.

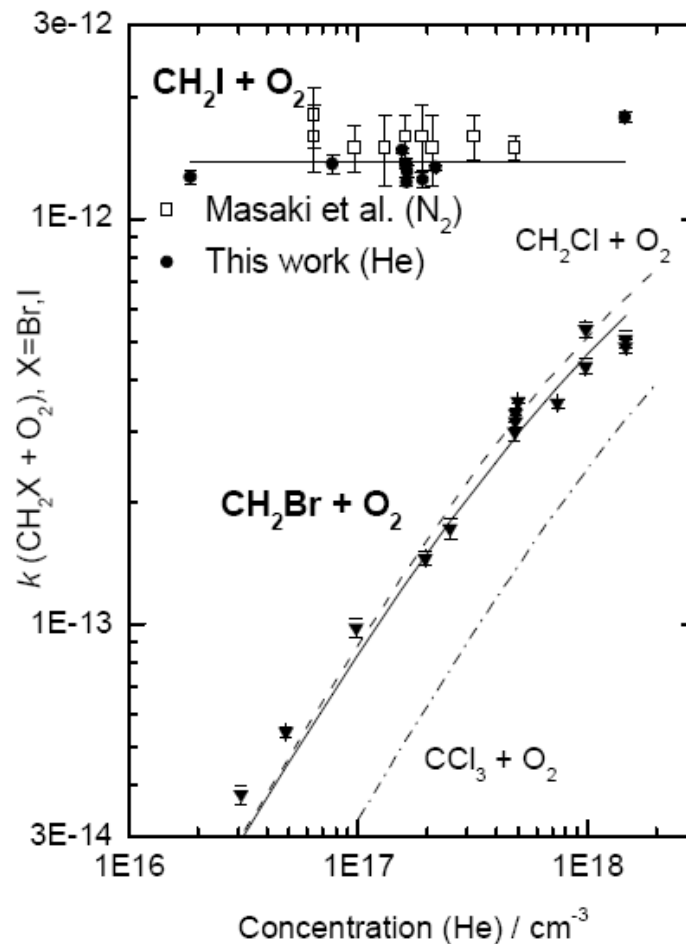
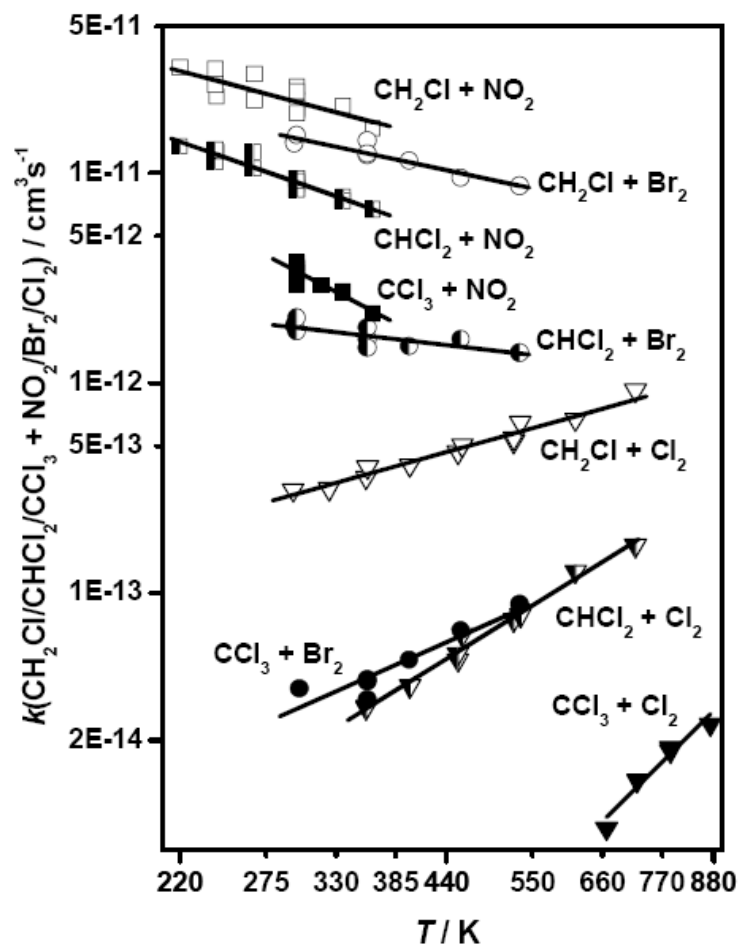


***Kinetic of enzymatic (catalytic) reaction***

The rate increases until a maximum value, then decreases.



# Temperature Dependence of Simple Gas Phase Radical Reactions

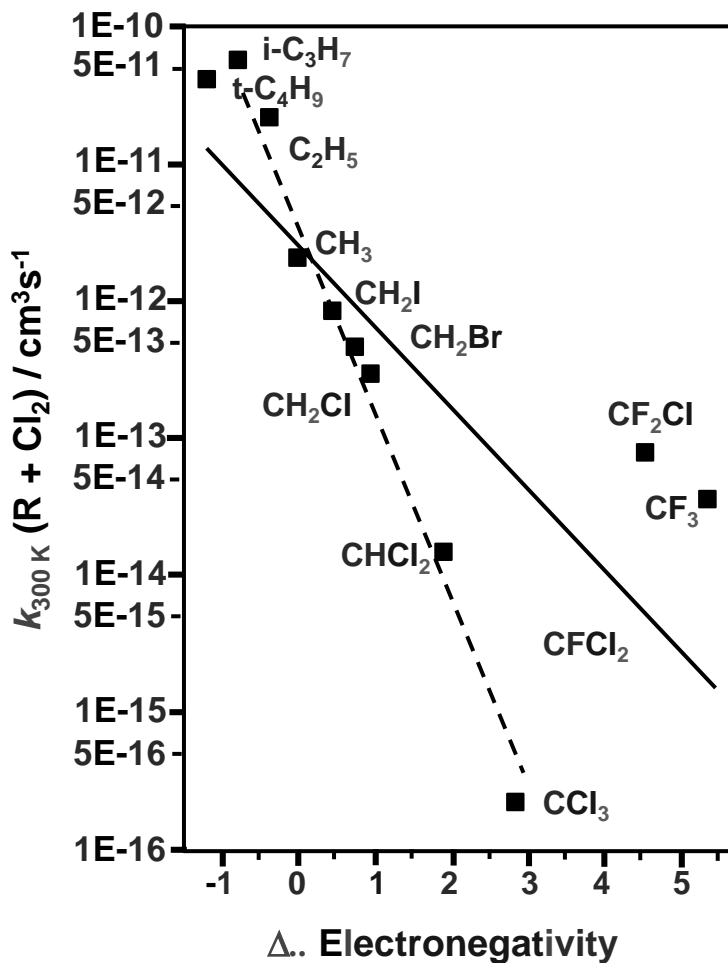


$$k(\text{CH}_3 + \text{HCl}) = (1.34 \pm 0.46) \times 10^{-14} (T/300 \text{ K})^{2.73 \pm 0.34} \exp[(387 \pm 99)\text{K}/T]$$

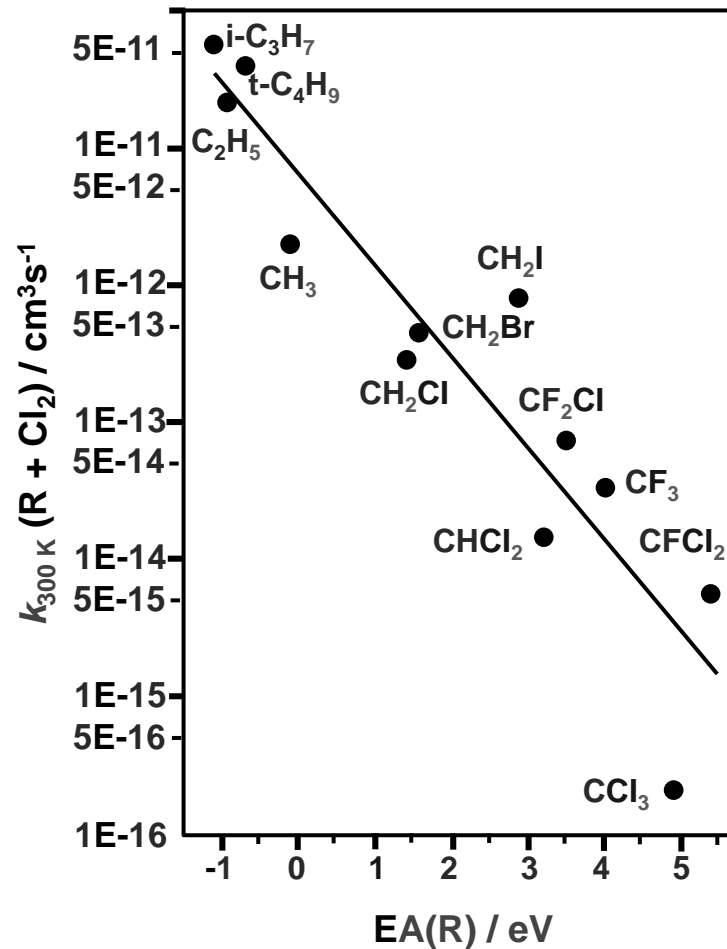




Logarithms of the room-temperature rate coefficients for the R + Cl<sub>2</sub> reactions *versus* Electronegativity (left) and EA(R) (right) of the radical.



$$\Delta \text{Electronegativity} = \sum_{i=1}^3 (X_i - X_H)$$

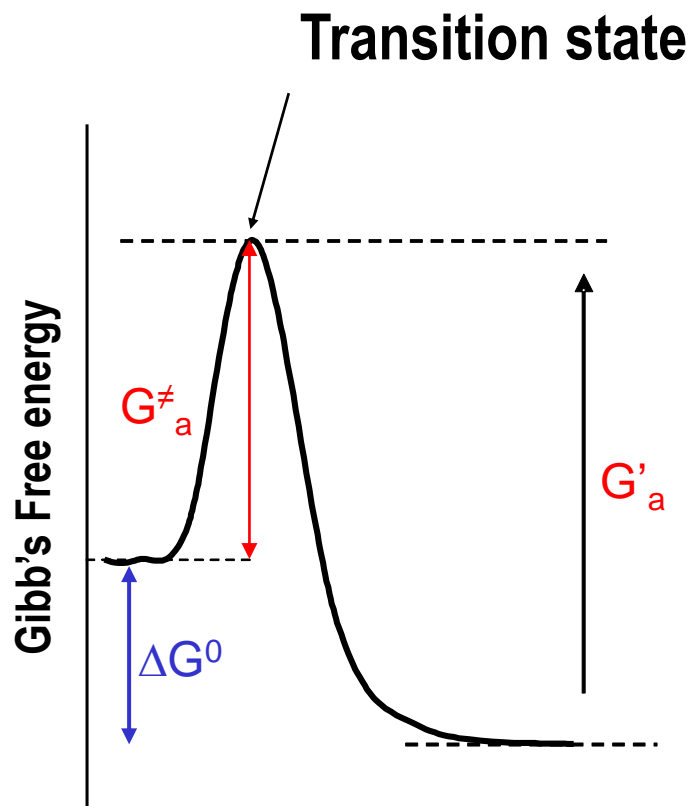


EA(R) = adiabatic electron affinity of the radical R.



# Reaction Mechanism

- **Reaction mechanism** describes the nature of the reaction route.
- Activated complex theory: the reactants in a reaction step come together in a loose structure of higher energy. The maximum is called the **transition state** and difference from the ground state is the **activation free energy**  $G_a^\ddagger$  of the reaction step.
- Note that the reverse step also has an activation energy ( $G_a^{\ddagger'}$ ), in this case higher than the forward step.
- The **molecularity** of a reaction step is the number of molecules coming together to react in that step
  - not the same as reaction order.





## Reaction Mechanisms

- The **mechanism** of a reaction is the sequence of individual events , known as **elementary steps**, that take the reactant molecule(s) to the product molecule(s).
- A **simple reaction** is one whose reaction mechanism consists of a single elementary step.
- Except for simple reactions, the overall balanced chemical equation gives no information on the mechanism.

### Example Ozone decomposition:

The conversion of ozone  $O_3$  to oxygen  $O_2$  has the overall balanced equation:



A possible mechanism for this reaction has two elementary steps:



Net result is the overall, balanced equation.  $O(g)$  is an **intermediate**.



## Intermediates and Determining Mechanisms

- A reaction **intermediate** is a species that appears in one or more elementary steps but not in the overall reaction.
- Thus an intermediate is generated in one or more elementary steps and consumed in others.
- The **stoichiometric number** of an elementary step is the number of times it must occur in the reaction mechanism in order to produce the correct overall chemical equation.
  
- A plausible **mechanism** for a given overall reaction is adopted as an hypothesis.
- A rate law for the overall reaction is then deduced from the proposed mechanism.
- This deduction is then compared with the known, experimental rate law for the overall reaction.
- A proposed reaction mechanism can be considered as valid only if it is consistent with the experimentally determined rate law.



# Catalysis

- A catalyst is a substance which increases the reaction rate by providing an alternate mechanism, one with a lower activation energy.
- The catalyst appears in one or more elementary steps of this mechanism, but not in the overall chemical reaction.
- Thus the catalyst remains intact after the reaction is complete.

## *Catalysis example:*

Overall reaction:

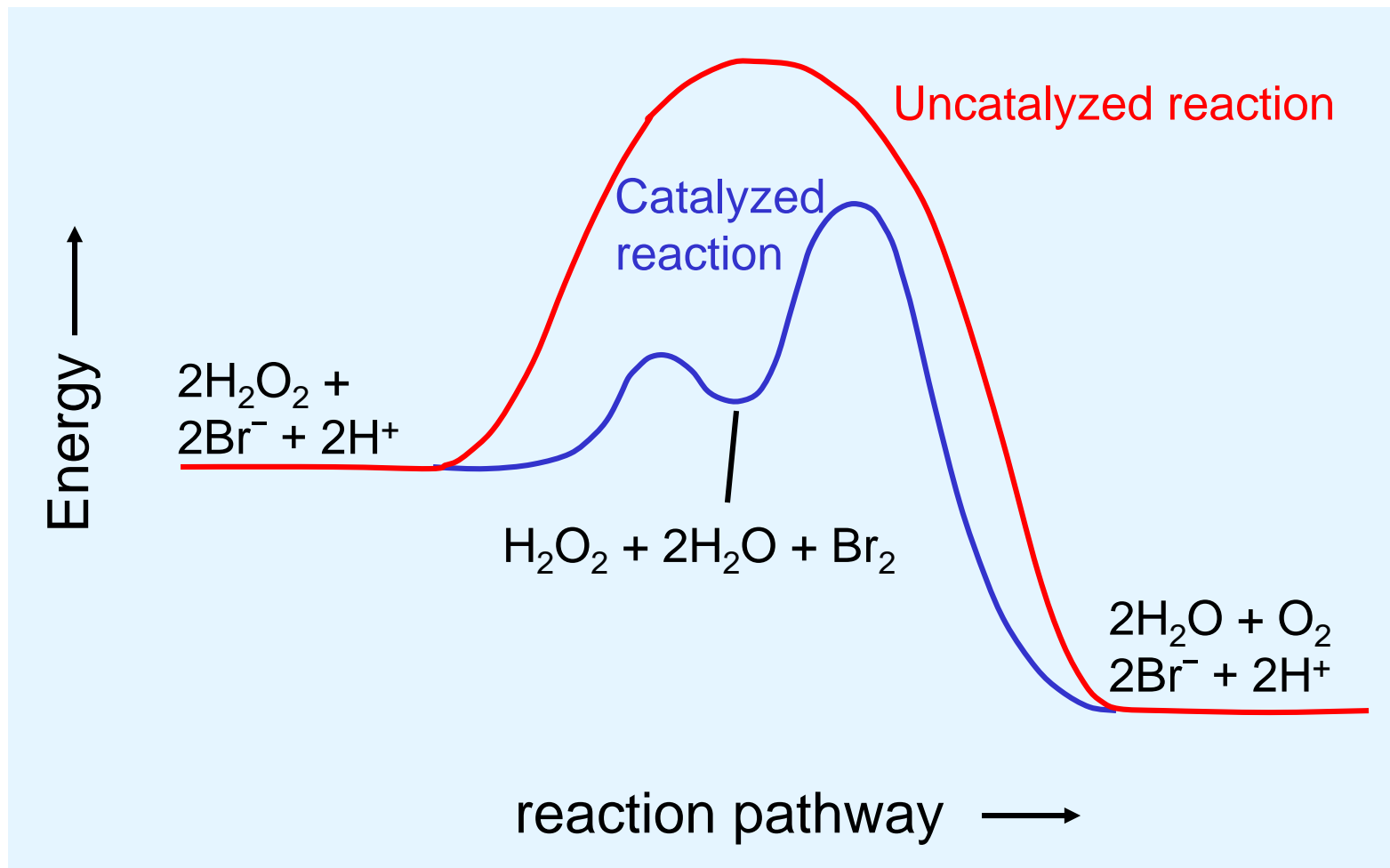


Mechanism for  $\text{Br}^-$ (aq) catalysis:





# Catalysis Profile





# Heterogeneous Catalysis

- Heterogeneous catalysts usually work by **adsorption** of the reactants on the surface of the phase of catalyst (commonly a solid).
- The places where the reactant molecules may be adsorbed are called **active sites**.
- Adsorption facilitates the breaking of bonds in the reactant molecules in order to form new ones.

## Langmuir Model

- Adsorption is complete once monolayer coverage has been reached.
- All adsorption sites are equivalent and the surface is uniform.
- The probability of adsorption or desorption at a site is independent of the occupancy state of adjacent sites.





# Langmuir Isotherm

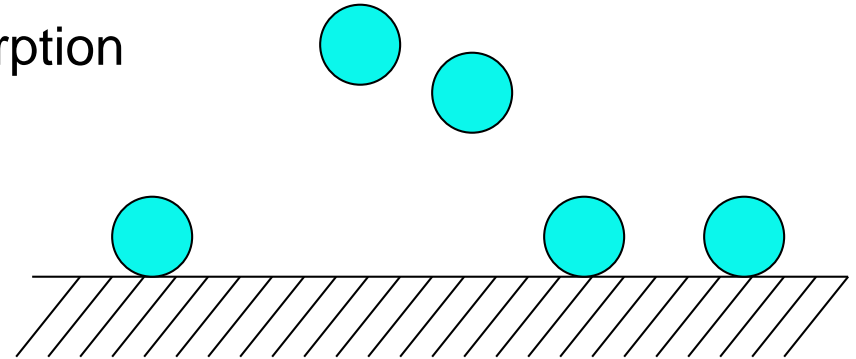
rate of adsorption

$$r_{ad} = \alpha p(1 - \theta)$$

rate of desorption

$$r_{des} = \alpha' \theta$$

rates are equal in equilibrium,  
with  $b = \alpha' / \alpha$



$$N = \frac{N_M P}{b + P} \quad \text{Langmuir isotherm}$$

$$\theta = \frac{N}{N_M}$$

$P$  = pressure

$\theta$  = coverage

$N$  = total number  
of adsorption  
sites

$$\frac{d\theta}{dt} = k_a P N (1 - \theta) - k_d N \theta = 0$$

$$\theta = \frac{KP}{KP + 1} \quad \text{where} \quad K = \frac{k_a}{k_d}$$

I. Langmuir, J. Am. Chem. Soc. 38 (1916) 2221





## Chemisorption

Unlike in physisorption, in chemisorption the adsorbed molecules undergo a chemical change:



The fractional coverage becomes

$$\theta = \frac{(KP)^{1/2}}{1 + (KP)^{1/2}}$$

In chemisorption the fractional coverage shows weaker pressure dependence than in physisorption.



# Free Radical Kinetics: First Order Reaction

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## First Order Reactions

- For a first order reaction the rate depends only from the concentration of a specific reagent :



$$v = -\frac{d}{dt}[A](t) = k_1 [A](t) \quad k_1, \text{ units } s^{-1}$$

$$\int_{[A]_0}^{[A]_t} \frac{d[A]}{[A]} = - \int_{t_0}^{t_t} k_1 dt, \quad \ln \frac{[A]_t}{[A]_0} = -k_1 (t - t_0)$$

Fundamental term: half life

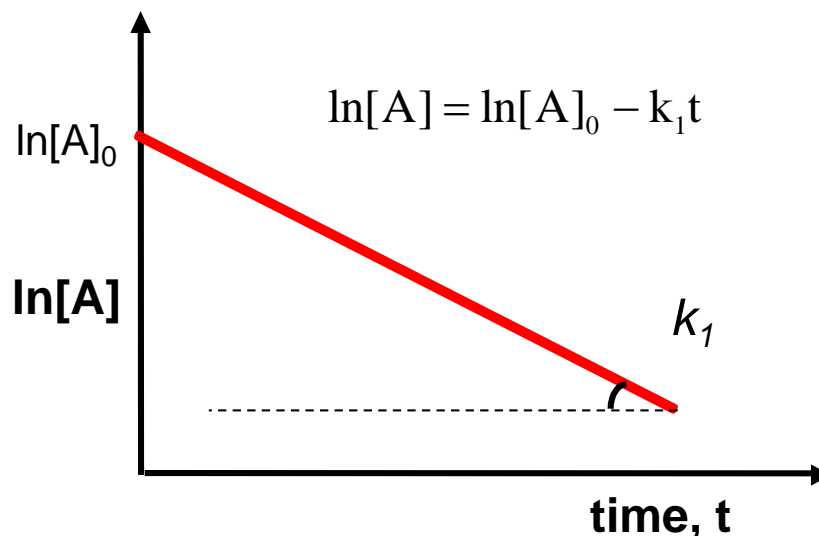


## First Order Kinetics

We can always postulate  $t_0 = 0$  :

$$\ln \frac{[A]_t}{[A]_0} = -k_1 (t - t_0) \longrightarrow \ln[A] = \ln[A]_0 - k_1 t$$

A plot of  $\ln[A]$  versus  $t$  allows to determine  $k_1$  (from the slope of the data interpolation line).



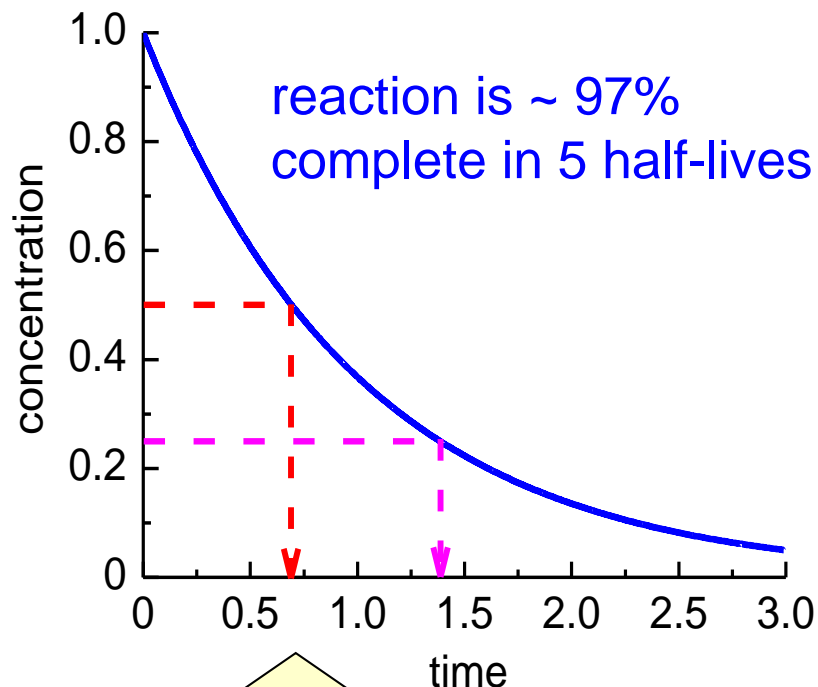
$$[A] = [A]_0 e^{-k_1 t}$$

If  $k$  in  $s^{-1}$ ,  $(\ln 2)/k$  is the half-life in seconds ( $t_{1/2}$ ).  $[A]$  halves each  $t_{1/2}$ .



## Many Radical Reactions are Exponential

- $A \rightarrow \text{product(s)}$ 
  - $t_{1/2} = \text{half-life}$   
 $= (\ln 2) / k$   
 $\approx 0.7 / k$
- $A + B \rightarrow \text{product(s)}$ 
  - Radical concentration much less than that of target?
  - If  $[B] \gg [A]$   
 $t_{1/2} \approx 0.7 / (k [B])$



Half-life does not change with concentration of A



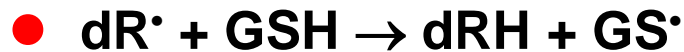
## Examples of Radical Lifetimes



$$k \approx 2.5 \times 10^9 \text{ M}^{-1} \cdot \text{s}^{-1}$$

If [deoxyribose] = 0.1 M

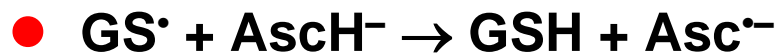
$$t_{1/2} \approx 3 \text{ ns } (\approx 0.7/(k [\text{dR}]))$$



$$k \approx 3.5 \times 10^7 \text{ M}^{-1} \cdot \text{s}^{-1}$$

If [GSH] = 5 mM

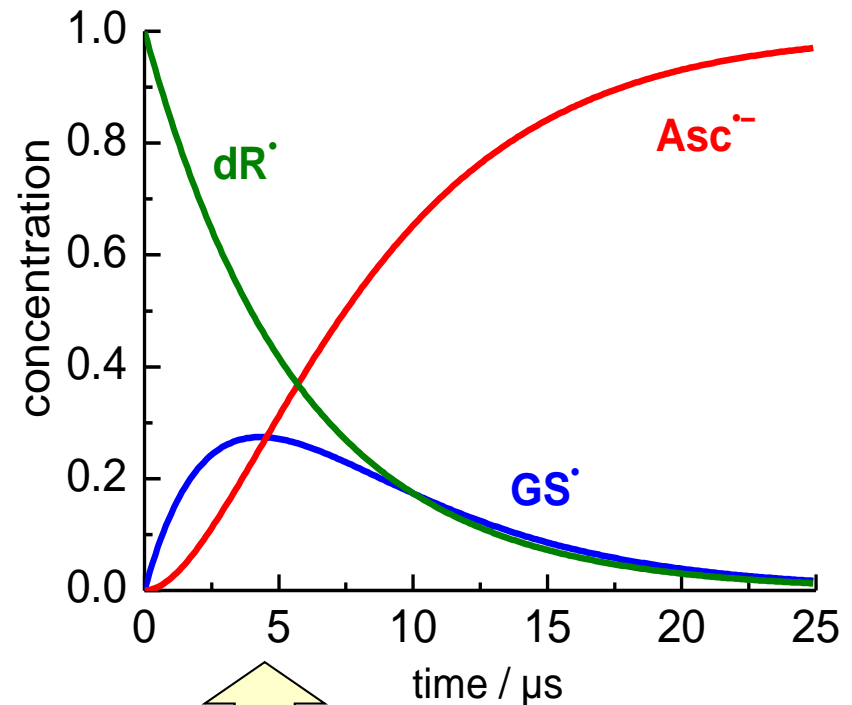
$$t_{1/2} \approx 4 \mu\text{s}$$



$$k \approx 6.0 \times 10^8 \text{ M}^{-1} \cdot \text{s}^{-1}$$

If [AscH<sup>-</sup>] = 0.5 mM

$$t_{1/2} \approx 2 \mu\text{s}$$



Intermediates in reaction cascade may have very low concentrations



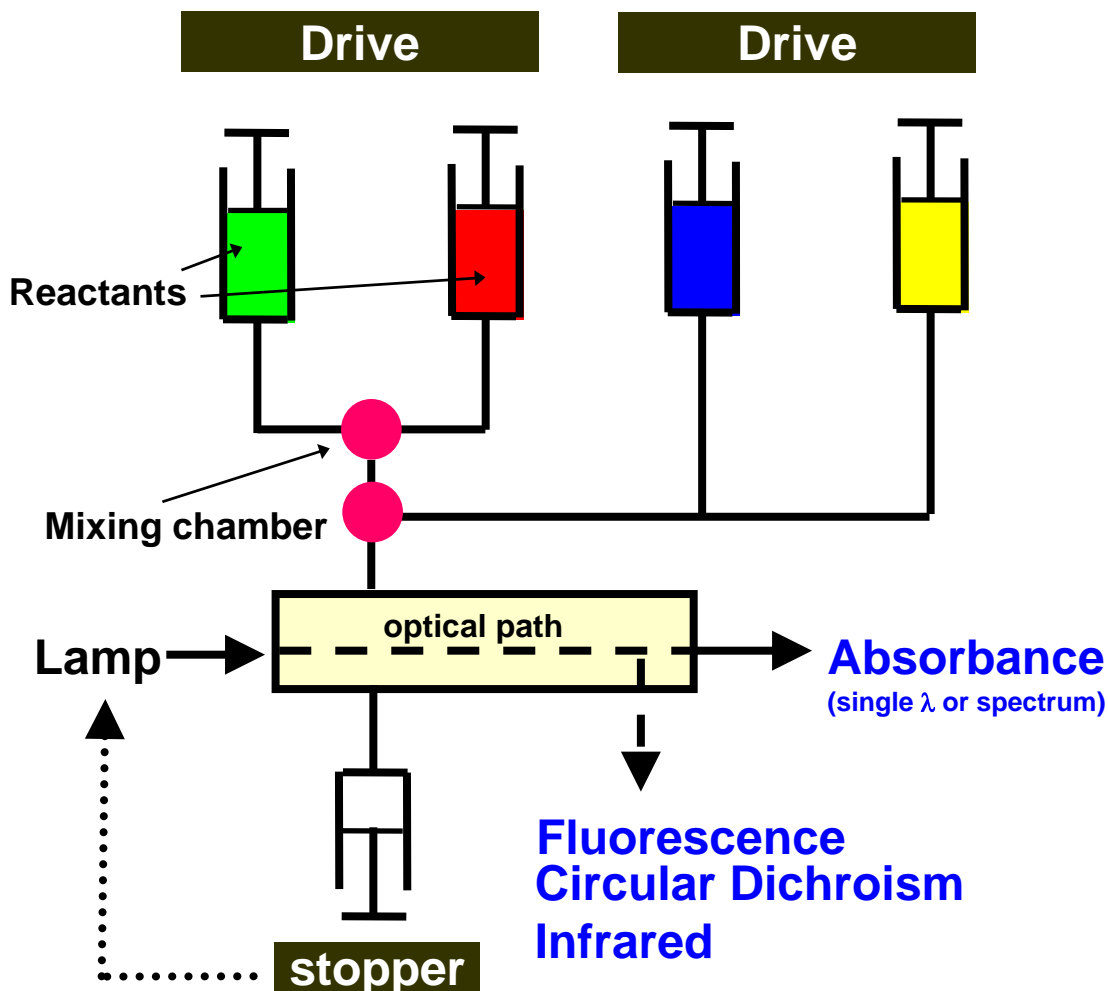
## Rate Constants of Radical/Fast Reactions

- Monitor **radical, reactant or product vs. time**
  - most radicals are short-lived, or reaction is fast
  - generate radicals in short time (pulse, flash)
  - needs high time resolution (micro- to milli-seconds)
- Measure **stable product** during/at end of reaction
  - two competing reactions (known reference)
- Measure **concentrations at steady-state**
  - needs information about competing reactions
  - steady-state concentrations may be extremely low

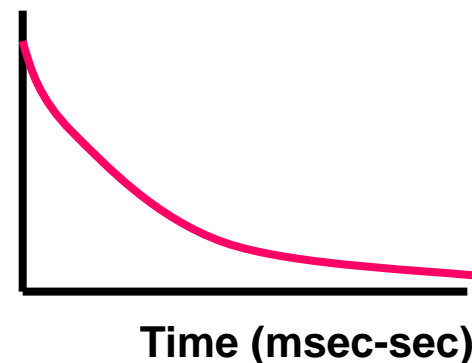


# Monitoring Rapid Reactions: Stopped-Flow Spectroscopy

## Schematic Representation of Stopped Flow Apparatus



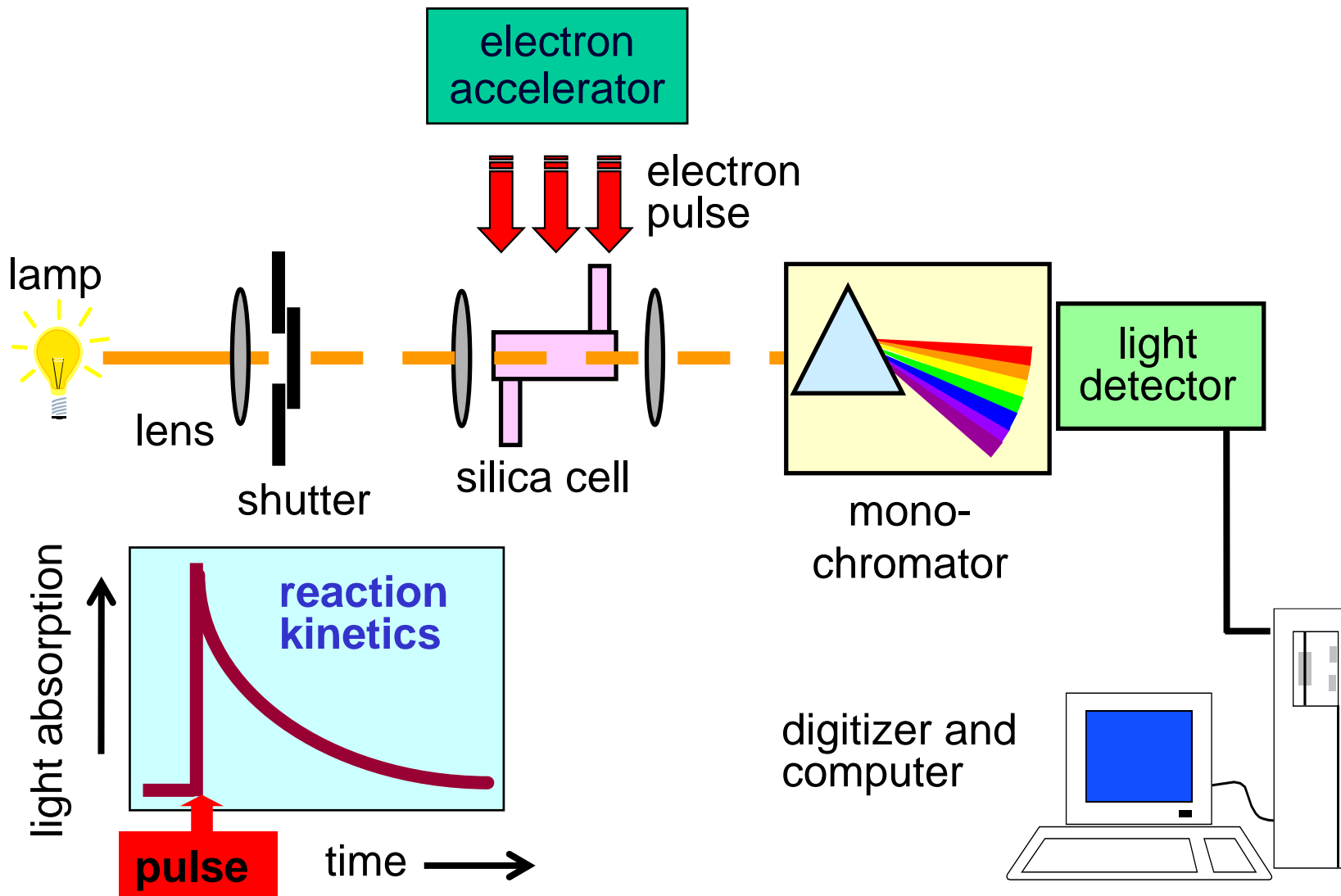
Time resolution limited to about 1 ms by interval between mixing and observation







# Pulse Radiolysis



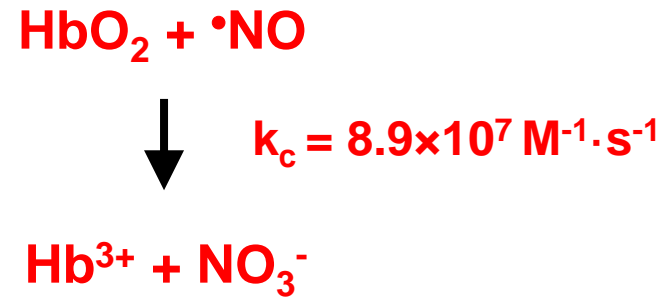
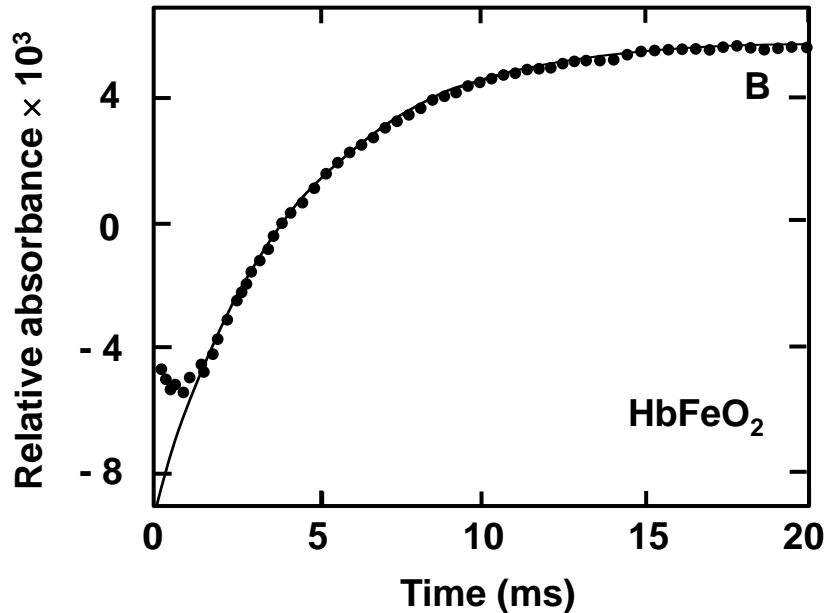


## Compilations of Rate Constants (Solution)

- University of Notre Dame  
Radiation Chemistry Data Center
  - web databases from compilations published in the *Journal of Physical and Chemical Reference Data*
  - [http://www.rcdc.nd.edu/browse\\_compil.html](http://www.rcdc.nd.edu/browse_compil.html)
  - <http://kinetics.nist.gov/solution/index.php>



# Example: $\cdot\text{NO}$ Dependent Oxidation of Oxyhemoglobin



Herold et al, Biochemistry, 40, 3385 (2001).

## Advantages

- monitor rapid (e.g. enzyme catalyzed reactions)  
(e.g. free radical/oxidant reactions)

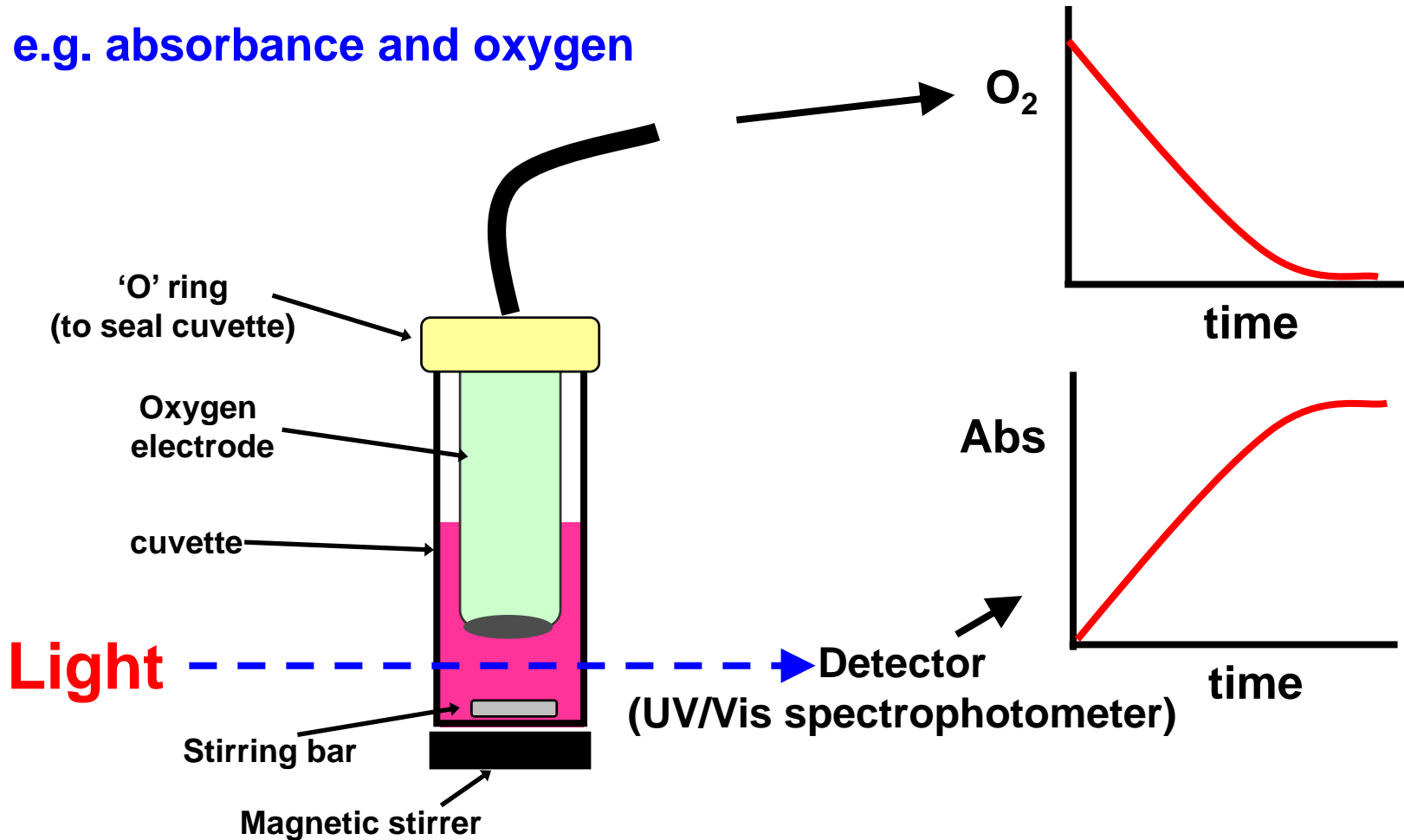
## Disadvantages

- expensive
- lag (dead) time (1-3 millisec)



# Combination of Approaches - Simultaneous Measurements

e.g. absorbance and oxygen

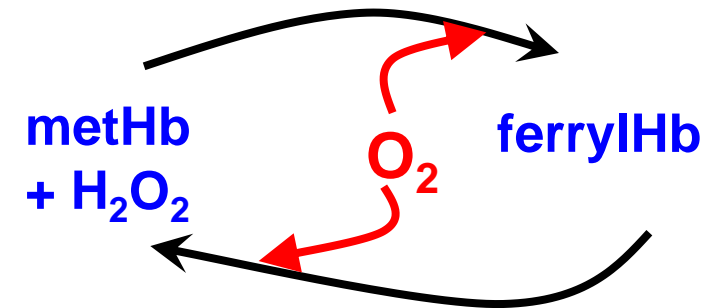
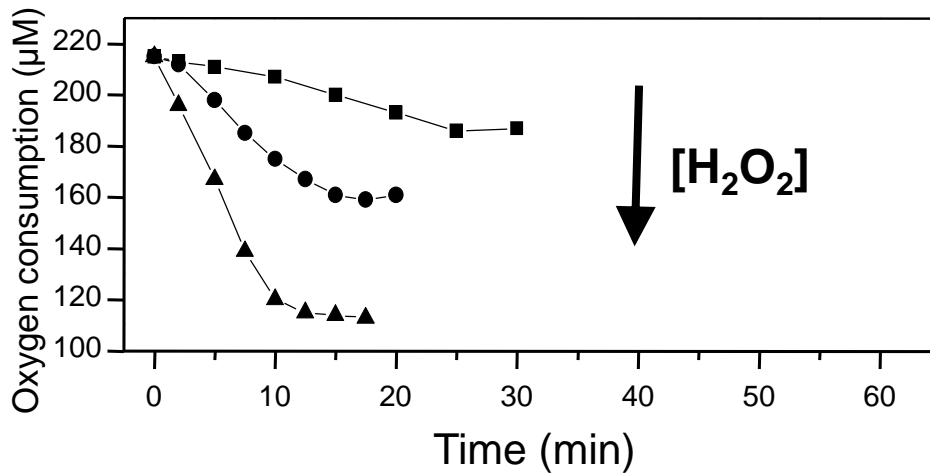
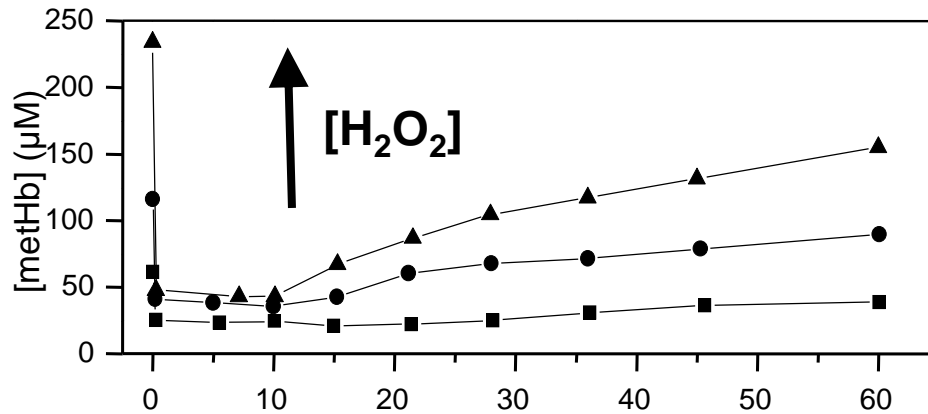


- Other polarographic e.g. NO electrode



## Example

- Simultaneous monitoring of absorbance spectrum and oxygen concentration:





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# Free Radical Kinetics: Second Order Reaction

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## Second Order Reactions



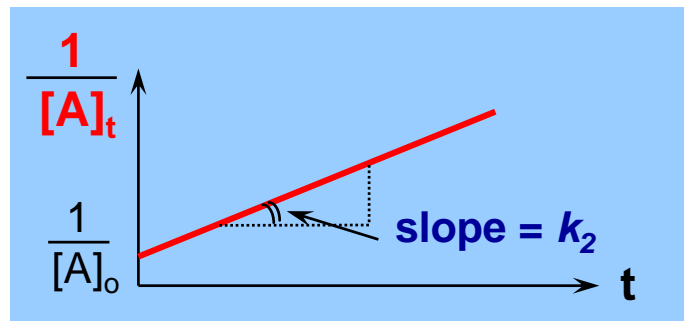
$k_2$  Unit :  $M^{-1} \cdot s^{-1}$

### 1) Class I.

$$v = -\frac{d[A]}{dt} = k_2 [A]^2$$

$$\int_{[A]_0}^{[A]_t} \frac{d[A]}{[A]^2} = - \int_0^t k_2 dt' \rightarrow \frac{1}{[A]_t} - \frac{1}{[A]_0} = k_2 t \rightarrow$$

$$\rightarrow \boxed{\frac{1}{[A]_t} = k_2 t + \frac{1}{[A]_0}}$$





## Half-life for a Second Order Reaction

The half-life of A ( $t_{1/2}$ ) can be deduced from:  $[A] = \frac{[A]_0}{2}$

$$[A] = \frac{[A]_0}{([A]_0 k_2 t + 1)} \longrightarrow \frac{2}{[A]_0} = k_2 t_{1/2} + \frac{1}{[A]_0}$$

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

For a second order reaction

$$t_{1/2} = \frac{\ln 2}{k_1}$$

Compare with a 1<sup>th</sup> order

The half-life for a second order reaction depends on the starting reagent concentration.





## Second Order Reaction (Class II)



$c_0A$ ,  $c_0B$  starting concentrations

$x = (\text{amount} / V)$  of reacted A

$(c_0A - x) = [A]$  at time  $t$

$$\frac{dx}{dt} = \frac{d[A]}{dt} = k (c_0A - x) \cdot (c_0B - x)$$

$$\frac{dx}{(c_0A - x) \cdot (c_0B - x)} = k dt$$

$$1 / [(c_0A - x) \cdot (c_0B - x)] = C / [c_0A - x] + D / [c_0B - x]$$

$$1 = D [c_0A - x] + C [c_0B - x] \quad \text{or} \quad 1 = D c_0A + C c_0B \quad 0 = D x + C x$$

Hence  $C = -D$  e  $1 / (c_0A - c_0B) = D$  (only if starting conc. different)

$$-dx / [c_0A - x] + dx / [c_0B - x] = (c_0A - c_0B) k dt = k dt$$

$$\ln [c_0A - x] - \ln [c_0B - x] = k dt \quad \text{or} \quad (c_0A - x) / (c_0B - x) = e^{kt} \quad \text{per } c_0A \neq c_0B$$



# Summary of Kinetic Law for Simple Kinetics

Reaction	Order	Kinetic Eq.	Integrated form	Unit
$A \rightarrow B$	Zero	$-d[A]/dt = 0$	$[A] = [A]_0 - kt$	$\text{mol l}^{-1}$
$A \rightarrow B$	First	$-d[A]/dt = k[A]$	$\ln[A]_t = -kt + \ln[A]_0$	$\text{s}^{-1}$
$A + A \rightarrow B$	Second	$-d[A]/dt = k[A]^2$	$\frac{1}{[A]_t} = k \cdot t + \frac{1}{[A]_0}$	$\text{l mol}^{-1}\text{s}^{-1}$
$A \rightleftharpoons B$	First	$-d[A]/dt = k_1[A] - k_{-1}[B]$		$\text{s}^{-1}$
$A + B \rightarrow P$	Second	$-d[A]/dt = k_1[A][B]$		$\text{l mol}^{-1}\text{s}^{-1}$

$$\ln \frac{[A]_0}{1/2[A]_0} = k \cdot t_{1/2}$$

$$t_{1/2} = \ln(2)/k \quad (\text{life-time})$$

$$t_{1/2} = 1/k[A]_0$$



# Competition Kinetics: Relative Rate Constants

- Two competing reactions:



- Measure yield of P at any time:

$$[P] \propto \frac{\text{rate of reaction of } R^\bullet \text{ producing P}}{\text{sum of rates of all competitive reactions of } R^\bullet}$$

$$[P] = [P]_0 \frac{k_1 [R^\bullet] [A]}{k_1 [R^\bullet] [A] + k_2 [R^\bullet] [B]} \quad [P]_0 = \text{yield in absence of B}$$

$$\frac{[P]_0}{[P]} = 1 + \frac{k_2 [B]}{k_1 [A]}$$

**Plot  $[P]_0 / [P]$  vs.  $[B] / [A]$   
slope = rate constant *ratio*  $k_2 / k_1$**

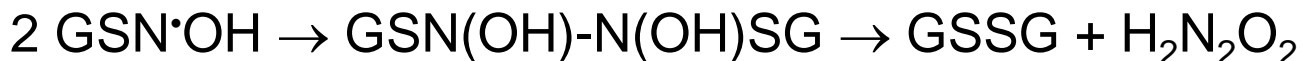
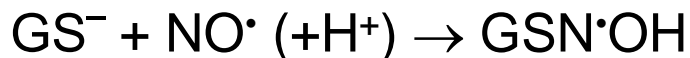


## Rate-limiting Steps

- Many reactions involve multiple steps
  - overall reaction rate may reflect the slowest or *rate-determining* step

- Example: **reaction of NO<sup>•</sup> with GSH**

- complex reaction forming GSSG and N<sub>2</sub>O
- reaction *may* involve:

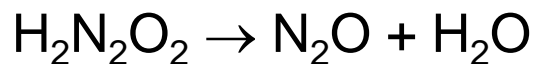


- may obtain apparently different kinetics depending on whether loss of NO<sup>•</sup>, loss of GSH, or formation of N<sub>2</sub>O is measured, and on the concentrations of reactants

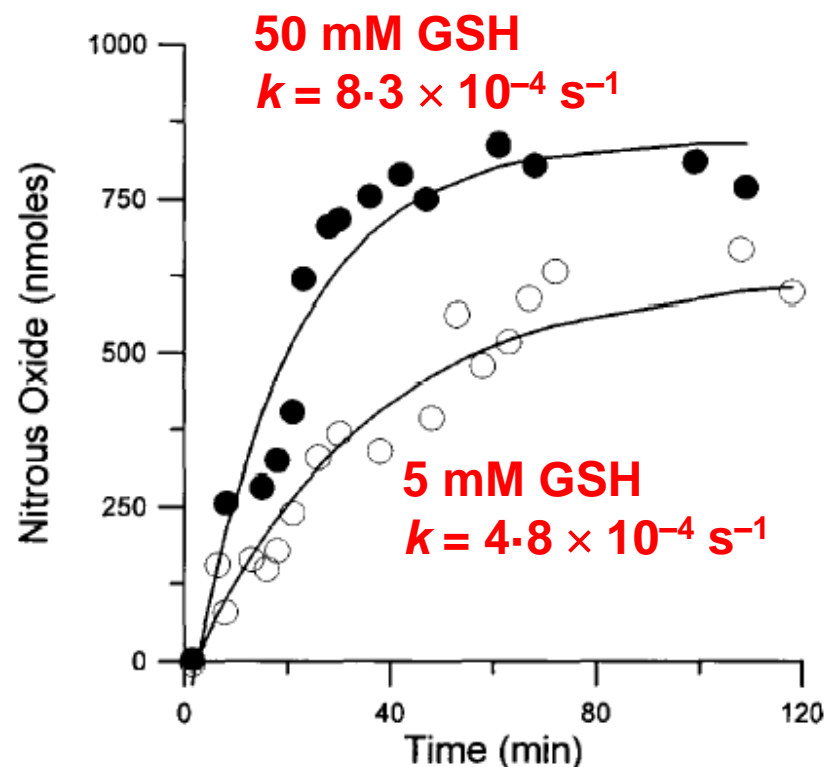


## Reaction of NO<sup>•</sup> with GSH: N<sub>2</sub>O Formation

- Hogg *et al.*\* measured N<sub>2</sub>O, with [GSH] >> [NO<sup>•</sup>]: but rate not proportional to [GSH] at high [GSH]
- Possible explanation: hyponitrite decomposition becoming rate-limiting
- Hughes and Stedman† measured pH and temperature dependence for:



$k \approx 2\text{--}3 \times 10^{-3} \text{ s}^{-1}$  at pH 7.4, 37°C




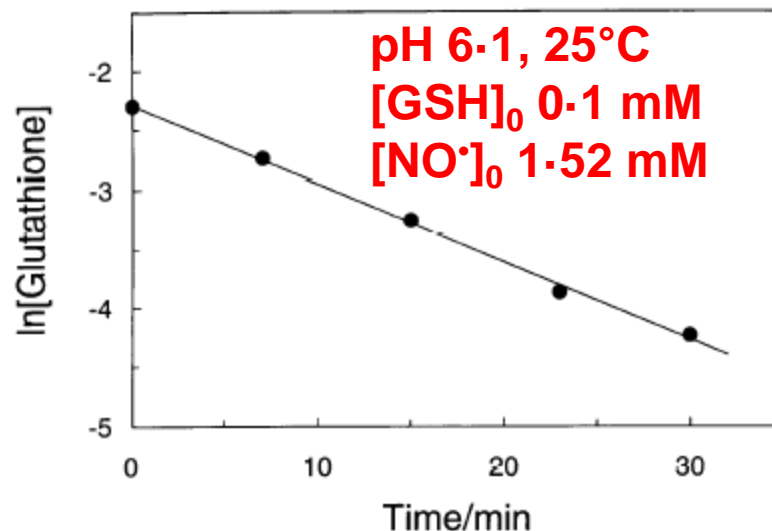
\* *FEBS Lett.*, **382**, 223 (1996)

† *J. Chem. Soc.* 129 (1963)



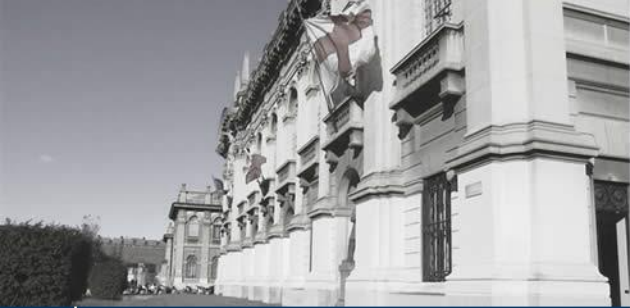
## Reaction of NO<sup>•</sup> with GSH: GSH Loss

- Aravindakumar *et al.*\* measured loss of GSH with [NO<sup>•</sup>] >> [GSH]
- pH-Dependence indicated GS<sup>-</sup> was reactive form 
- Rate constant for GS<sup>-</sup> + NO<sup>•</sup> = 490 M<sup>-1</sup> s<sup>-1</sup> at 25°C (effective rate constant ~ 14 M<sup>-1</sup> s<sup>-1</sup> at pH 7.4 since [GS<sup>-</sup>] ≈ 3% of [GSH]<sub>total</sub>)
- $t_{1/2}$ (NO<sup>•</sup>) ~ 10 s with 5 mM GSH at pH 7.4, 25°C



**Reactivity ~ 100-fold faster than suggested from study of Hogg *et al.* (1996)**

\* *J. Chem. Soc., Perkin Trans. 2*, 663 (2002)



 POLITECNICO DI MILANO

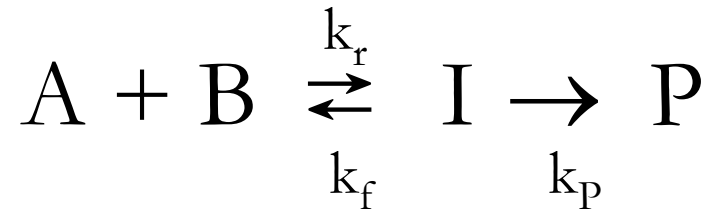


# Free Radical Kinetics: Steady State

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Dipartimento CMIC “Giulio Natta”



## Preequilibrium Approximation



$$k_f [A][B] = k_r [I]$$

$$\frac{[I]}{[A][B]} = \frac{k_f}{k_r} = K_c \Rightarrow [I] = K_c [A][B]$$

$$rate = k_p [I] = k_p K_c [A][B]$$





## Preequilibrium Example

Find the overall rate law for the mechanism:



$$\text{rate} = k_p [\text{N}_2\text{O}_2] [\text{Br}_2]$$

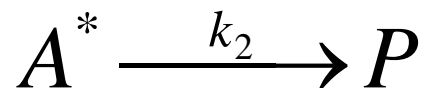
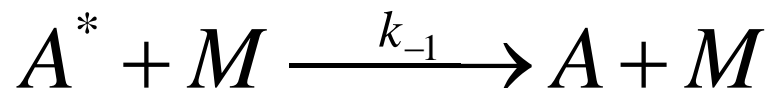
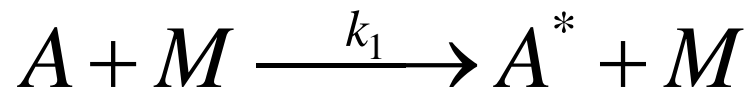
$$k_1 [\text{NO}]^2 = k_{-1} [\text{N}_2\text{O}_2] \Rightarrow [\text{N}_2\text{O}_2] = K_c [\text{NO}]^2$$

$$\text{rate} = (k_p K_c) [\text{NO}]^2 [\text{Br}_2] = k_{\text{eff}} [\text{NO}]^2 [\text{Br}_2]$$



## Lindemann Mechanism

for unimolecular reaction  $A \rightarrow P$



$A^*$  is the **activated reactant**, produced by collisions with a spectator species  $M$ .

$A^*$  is then either deactivated by another collisions or transformed into the product  $P$ .



## Lindemann Rate Law

using the steady state approximation

$$\frac{d[A^*]}{dt} = k_1[A][M] - k_{-1}[M][A^*] - k_2[A^*] = 0$$

$$\therefore [A^*] = \frac{k_1[A][M]}{k_{-1}[M] + k_2}$$

$$\frac{dP}{dt} = k_2[A^*] = \frac{k_2k_1[A][M]}{k_{-1}[M] + k_2}$$

$$\frac{dP}{dt} = \frac{k_2k_1[A][M]}{k_{-1}[M] + k_2} = k_{uni}[A]$$

$$k_{uni} = \frac{k_2k_1[M]}{k_{-1}[M] + k_2} = \frac{k_2k_1}{k_{-1} + k_2/[M]}$$

- $1/k_{uni}$  vs.  $1/[M]$  is linear with a slope of  $1/k_1$  and intercept  $k_{-1}/k_1k_2$
- In the limit of high  $[M]$ , the rate is first order in  $[A]$  with rate constant  $k_1k_2/k_{-1}$

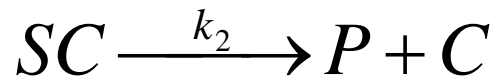
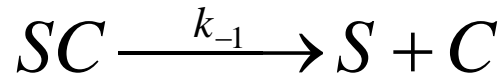
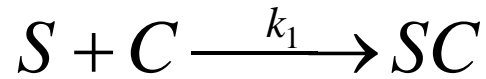


## Reversible Reactions: Driving Uphill

- An unfavourable reaction can be driven by removal of a product from the equilibrium
- Le Chatelier's principle (1884, rephrased 1888):  
'Every change of one of the factors of an equilibrium occasions a rearrangement of the system ... in a sense opposite to the original change.'
- Example:  $A + B \rightleftharpoons C + D$ 
  - If forward rate  $<$  reverse rate, equilibrium is to left, i.e. if  $k_f [A] [B] < k_r [C] [D]$
  - but if C or D is removed by another reaction, equilibrium can be driven to the right



## Substrate-Complex Kinetics



- $S$  is the substrate to which the catalyst  $C$  binds.
- $SC$  is the substrate-catalyst complex.
- $P$  is the product

$$\frac{d[SC]}{dt} = k_1[S][C] - k_{-1}[SC] - k_2[SC] = 0$$

$$[SC] = \frac{k_1[S][C]}{k_{-1} + k_2} \equiv \frac{[S][C]}{K_m}$$

$$rate = k_2[SC] = \frac{k_2[S][C]}{K_m}$$

$$K_m = \text{composite constant} = \frac{k_{-1} + k_2}{k_1}$$



## Conservation of Mass

$$[S] = [S]_0 - [SC] - [P]$$

$$[C] = [C]_0 - [SC]$$

for low SC and  
product  
concentrations

$$K_m [SC] = ([S]_0 - [SC] - [P])([C]_0 - [SC])$$

$$[SC] \approx \frac{[S]_0 [C]_0}{[S]_0 + [C]_0 + K_m}$$

Initial Reaction Rate

$$R_0 = \frac{k_2 [S]_0 [C]_0}{[S]_0 + [C]_0 + K_m}$$

if  $[S]_0 \gg [C]_0$ , then  $R_0 = \frac{k_2 [S]_0 [C]_0}{[S]_0 + K_m}$

Reciprocal plot:  
 $1/R_0$  vs.  $1/[S]_0$  is linear

$$\frac{1}{R_0} = \frac{1}{k_2 [C]_0} + \left( \frac{K_m}{k_2 [C]_0} \right) \frac{1}{[S]_0}$$



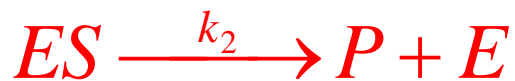
# Maximum Reaction Rate and Enzyme Kinetics

$$R_0 = \frac{k_2[S]_0[C]_0}{[S]_0 + K_m}$$

For  $[S]_0 \gg K_m$ ,  $R_0 = k_2[C]_0 = R_{\max}$

As the substrate concentration is increased, the initial rate of reaction approaches a limiting maximum,  $R_{\max}$ .

## Michaelis-Menten Mechanism



- E is an enzyme, which acts as a catalyst.
- S is the substrate
- ES is the complex.
- P is the product.



## Michaelis-Menten Rate Law

$$R_0 = \frac{k_2[S]_0[E]_0}{[S]_0 + K_m}$$

$$\frac{1}{R_0} = \frac{1}{R_{\max}} + \frac{K_m}{R_{\max}} \frac{1}{[S]_0}$$

Where  $R_{\max} \equiv k_2[E]_0$

Lineweaver-Burk plot:  $1/R_0$  vs.  $1/[S]_0$  is linear

$$\text{slope} = \frac{K_m}{R_{\max}} \text{ and intercept} = \frac{1}{R_{\max}}$$

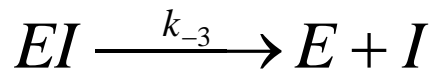
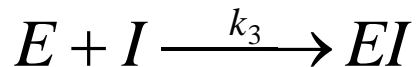
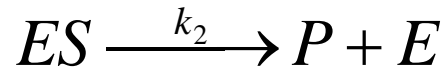
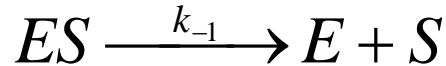
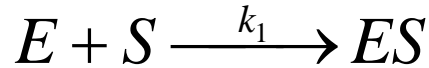
$$K_m = \frac{\text{slope}}{\text{intercept}} \text{ and } k_2 = \frac{1}{[E]_0 \times \text{intercept}}$$

$k_2$  = turnover number





## Competitive Inhibition



- $I$  is an inhibitor that competes with  $S$  to bind to the enzyme  $E$ .
- $EI$  is the enzyme-inhibitor complex.

Rate Law: 
$$R_0 = \frac{k_2[S]_0[E]_0}{[S]_0 + K_m^*}$$

$$K_m^* = K_m \left( 1 + \frac{[I]}{K_I} \right) \text{ and } K_I = \frac{[E][I]}{[EI]}$$

$$\frac{1}{R_0} = \frac{1}{R_{\max}} + \frac{K_m^*}{R_{\max}} \frac{1}{[S]_0} \quad \text{slope} = \frac{K_m^*}{R_{\max}} \text{ where } K_m^* = K_m \left( 1 + \frac{[I]}{K_I} \right)$$

The slope increases with  $[I]$ , indicating that  $I$  is an inhibitor.



## Types of Catalysis

A **homogeneous catalyst** is present in the same phase as species involved in the reaction.

A **heterogeneous catalyst** is in a different phase from reacting species, often a solid.

- solid, heterogeneous catalysis proceeds via **physisorption**, the adsorption of reacting molecules onto the surface of the catalyst, without changing their internal bonding or via **chemisorption**, the formation of chemical bonds between the reagent and **active sites** on the catalyst surface.
- the **fractional coverage**  $\theta$  is the proportion of possible absorption sites that are actually occupied.



## Ozone Depletion: Uncatalyzed

- The conversion of ozone  $O_3$  to oxygen  $O_2$  has the overall balanced equation:



- A possible **mechanism** for this reaction has two **elementary steps**:



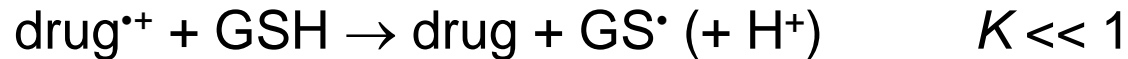
- The rate law is (with no catalyst):

$$R_{nc} = k_{nc} [O][O_3]$$

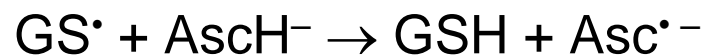
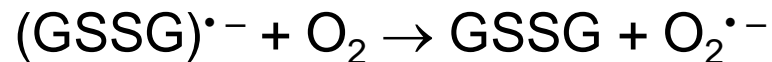
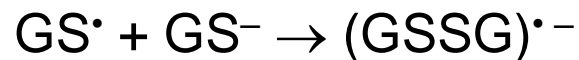


# Product Removal can Drive an Unfavourable Equilibrium

- Glutathione often 'repairs' drug radicals more efficiently than redox properties predict:

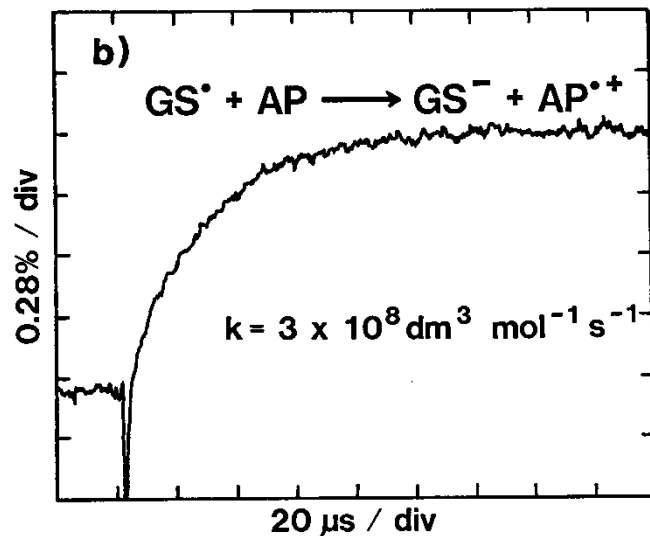
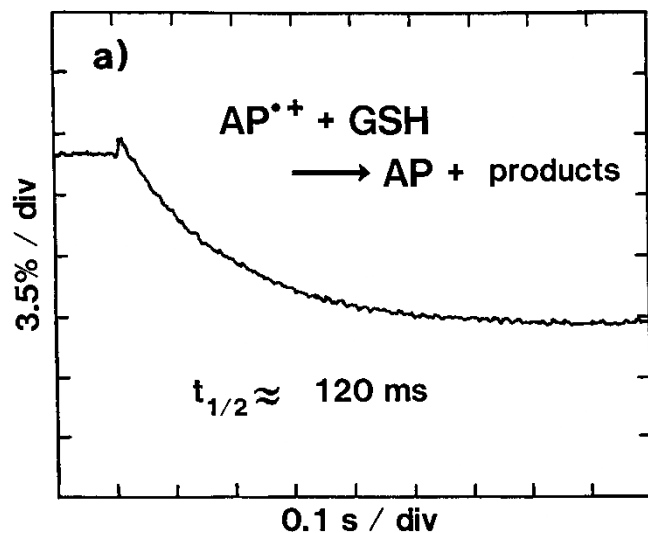


- Drug radical often much weaker oxidant than  $\text{GS}^{\bullet}$
- Removal of product ( $\text{GS}^{\bullet}$ , e.g. by  $\text{O}_2$  or ascorbate) drives unfavourable equilibrium to the right

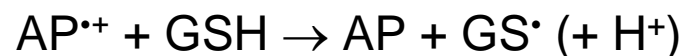




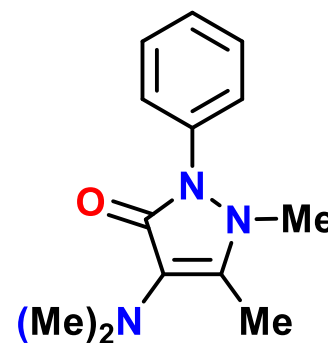
## Unfavourable Radical 'Repair' by GSH



The radical-cation of aminopyrine (structure below) reacts rapidly with GSH:



$K < 10^{-4}$  yet reaction proceeds in  $< 1 \text{ s}$  because  $GS^{\bullet}$  is removed from the equilibrium

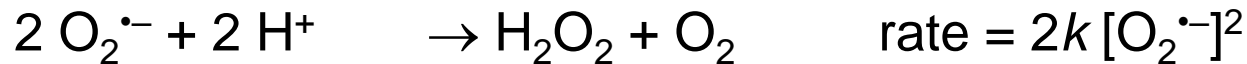


Wilson *et al.*, *Biochem. Pharmacol.*, **35**, 21 (1986)



## Steady-state Concentrations

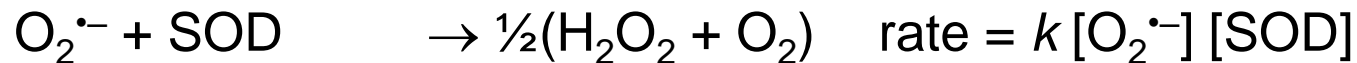
- At a steady-state, **rate of formation = rate of loss**
- Superoxide radicals, no superoxide dismutase:



$$\text{At steady-state: } 6 \times 10^{-7} = 2.4 \times 10^5 [\text{O}_2^{\bullet-}]^2$$

$$[\text{O}_2^{\bullet-}] \approx \mathbf{1.6 \mu\text{M}}$$
 (n.b. here  $[\text{O}_2^{\bullet-}] = [\text{O}_2^{\bullet-}] + [\text{HO}_2^{\bullet}]$ )

- With 3  $\mu\text{M}$  superoxide dismutase (SOD):



$$\text{At steady-state: } 6 \times 10^{-7} = 2.3 \times 10^9 [\text{O}_2^{\bullet-}] \times 3 \times 10^{-6}$$

$$[\text{O}_2^{\bullet-}] \approx \mathbf{90 \text{ pM}}$$

Cadenas & Davies *Free Radical Biol. Med.*, 2000, **29**, 222



# Free Radical Kinetics: Chain Reaction

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Dipartimento CMIC “Giulio Natta”

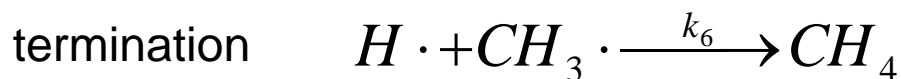
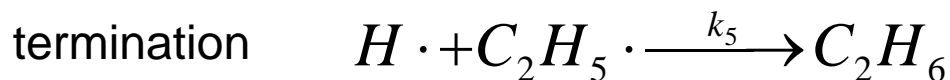
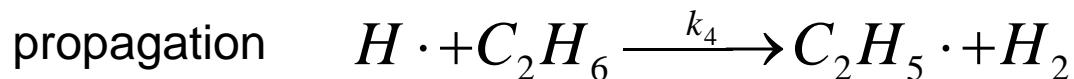
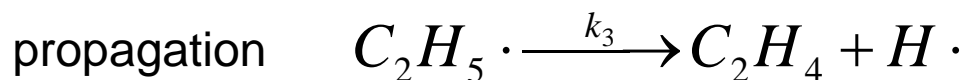
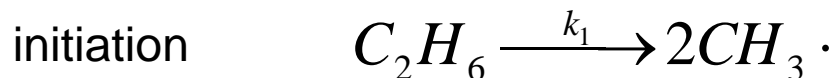


## Radical Chain Reactions

The mechanisms of radical chain reactions involve three kinds of elementary steps:

- **Initiation step:** produces radical(s) from reactants
- **Propagation step:** produces products and more radicals
- **Termination step:** radicals combine to form non-radical products.

Example:  $C_2H_6 \rightarrow C_2H_4 + H_2$







## Rate Law: $C_2H_6 \rightarrow C_2H_4 + H_2$

steady state approximation

$$[CH_3\cdot] = 2k_1 / k_2$$

$$[C_2H_5\cdot] = (k_1k_4 / k_3k_5)^{1/2} [C_2H_6]$$

$$[H\cdot] = (k_1k_3 / k_4k_5)^{1/2}$$

$$rate = \left( \frac{k_1k_3k_4}{k_5} \right)^{1/2} [C_2H_6]$$

first order in  $C_2H_6$

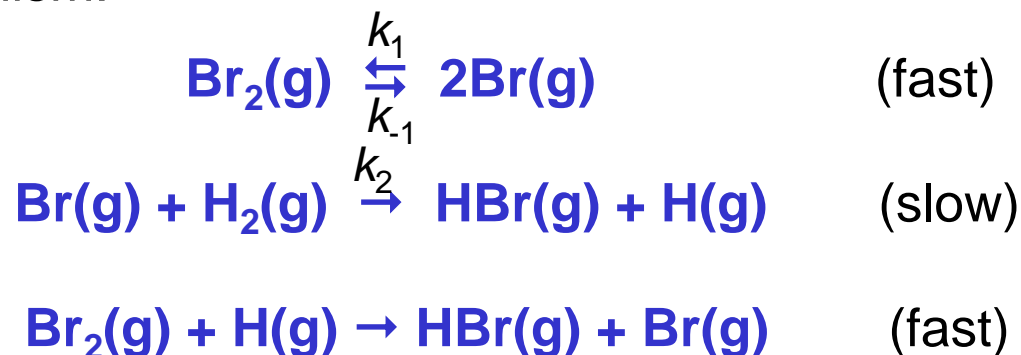


## HBr Example

Overall reaction:



Possible mechanism:



The overall rate law is:

$$\text{rate} = \frac{k_2 k_1}{k_{-1}} [\text{H}_2] [\text{Br}_2]^{\frac{1}{2}}$$

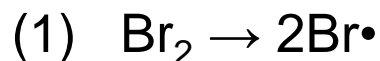


## More on Hydrogen – Bromine Reaction

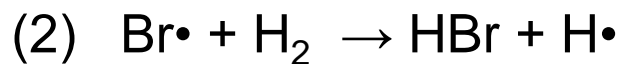
- Overall reaction  $\text{H}_2 + \text{Br}_2 \rightarrow 2\text{HBr}$
- Complex rate law suggests a complex mechanism.

$$\frac{d[\text{HBr}]}{dt} = \frac{k'[\text{H}_2][\text{Br}_2]^{3/2}}{[\text{Br}_2] + k''[\text{HBr}]}$$

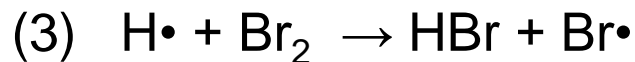
- Generally accepted mechanism



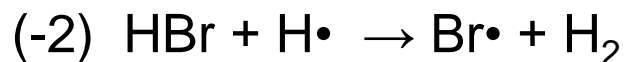
Initiation



Propagation



Propagation



Retardation



Termination

- Note that there are 2 radical intermediates  $\text{H}\cdot$  and  $\text{Br}\cdot$  (the **chain carriers**).
- We can apply the steady state hypothesis to both of them.



## Hydrogen – Bromine Reaction (cont.)

Eq (i) Overall rate

$$(i) \frac{d[\text{HBr}]}{dt} = k_2[\text{Br}\cdot][\text{H}_2] + k_3[\text{H}\cdot][\text{Br}_2] - k_{-2}[\text{H}\cdot][\text{HBr}]$$

Eq (ii) and Eq (iii):  
apply steady state  
approxm to  $[\text{H}\cdot]$   
and  $[\text{Br}\cdot]$ .

$$(ii) \frac{d[\text{H}\cdot]}{dt} = k_2[\text{Br}\cdot][\text{H}_2] - k_3[\text{H}\cdot][\text{Br}_2] - k_{-2}[\text{H}\cdot][\text{HBr}] = 0$$

$$(iii) \frac{d[\text{Br}\cdot]}{dt} = k_1[\text{Br}_2] - k_2[\text{Br}\cdot][\text{H}_2] + k_3[\text{H}\cdot][\text{Br}_2] + k_{-2}[\text{H}\cdot][\text{HBr}] - k_{-1}[\text{Br}\cdot]^2 = 0$$

Eq (iv): add Eq (ii)  
and Eq (iii).

$$(iv) \quad k_1[\text{Br}_2] - k_{-1}[\text{Br}\cdot]^2 = 0 \qquad (v) \quad [\text{Br}\cdot] = \left(\frac{k_1}{k_{-1}}\right)^{1/2} [\text{Br}_2]^{1/2}$$

Hence Eq (v) for  
 $[\text{Br}\cdot]$ .

$$(vi) \quad [\text{H}\cdot] = \frac{k_2(k_1/k_{-1})^{1/2} [\text{H}_2][\text{Br}_2]^{1/2}}{k_3[\text{Br}_2] + k_{-2}[\text{HBr}]}$$

Eq (vi): substitute for  
 $[\text{Br}\cdot]$  in Eq (ii) and  
solve for  $[\text{H}\cdot]$ .

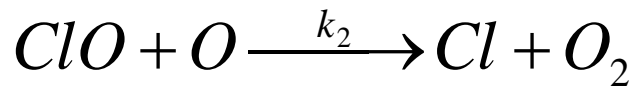
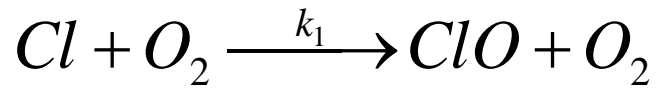
$$(vii) \quad \frac{d[\text{HBr}]}{dt} = k_2(k_1/k_{-1})^{1/2} [\text{Br}_2]^{1/2} [\text{H}_2] + k_3 \frac{k_2(k_1/k_{-1})^{1/2} [\text{H}_2][\text{Br}_2]^{1/2}}{k_3[\text{Br}_2] + k_{-2}[\text{HBr}]} [\text{Br}_2]$$

Eq (vii): substitute for  
 $[\text{H}\cdot]$  and  $[\text{Br}\cdot]$  in Eq  
(i), cancel out terms  
and rearrange.

$$\begin{aligned} & - k_{-2} \frac{k_2(k_1/k_{-1})^{1/2} [\text{H}_2][\text{Br}_2]^{1/2}}{k_3[\text{Br}_2] + k_{-2}[\text{HBr}]} [\text{HBr}] \\ & \quad \neq k_2(k_1/k_{-1})^{1/2} k_3[\text{Br}_2]^{3/2} [\text{H}_2] + \cancel{k_2(k_1/k_{-1})^{1/2} k_{-2}[\text{Br}_2]^{1/2} [\text{H}_2][\text{HBr}]} \\ & \quad + k_2 k_3 (k_1/k_{-1})^{1/2} [\text{H}_2][\text{Br}_2]^{3/2} - \cancel{k_{-2} k_2 (k_1/k_{-1})^{1/2} [\text{H}_2][\text{Br}_2]^{1/2} [\text{HBr}]} \\ & = \frac{\quad}{k_3[\text{Br}_2] + k_{-2}[\text{HBr}]} \\ & = \frac{2k_2(k_1/k_{-1})^{1/2} k_3[\text{Br}_2]^{3/2} [\text{H}_2]}{k_3[\text{Br}_2] + k_{-2}[\text{HBr}]} = \frac{k'[\text{H}_2][\text{Br}_2]^{3/2}}{[\text{Br}_2] + k''[\text{HBr}]} \end{aligned}$$



## Ozone Depletion: Catalyzed



$$[Cl] = \frac{k_2[X][O]}{k_1[O_3] + k_2[O]}$$

$$R_{cat} = k_1[Cl][O_3] = \frac{k_1 k_2 [X][O][O_3]}{k_1[O_3] + k_2[O]}$$

$$R_{cat} \approx k_2[X][O] \text{ since } [O_3] \gg [O]$$

### Catalyzed vs. Uncatalyzed:

$$R_{nc} = k_{nc} [O][O_3]$$

$$R_{cat} = k_2 [O][X]$$

$$R_{cat}/R_{nc} = \frac{k_2[X]}{k_{nc}[O_3]} \approx 74$$

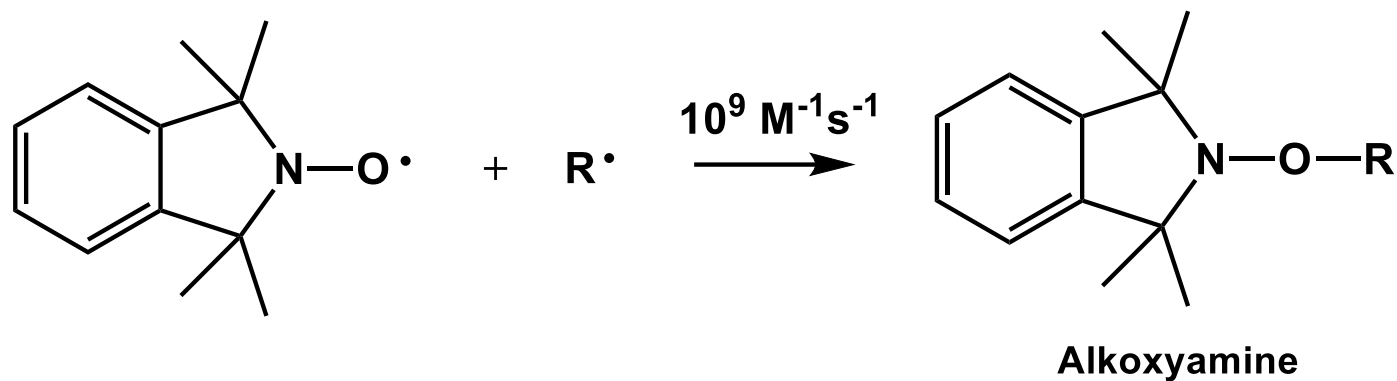


# Free Radical Kinetics: Redox Chain Reaction

Prof. Attilio Citterio  
Dipartimento CMIC “Giulio Natta”

# Nitroxides are used as radical traps of carbon-centred radicals

## Identifying reactive radicals and studying radical reactions





 POLITECNICO DI MILANO



# Free Radical Kinetics: **Inhibition**

Prof. Attilio Citterio  
Dipartimento CMIC “Giulio Natta”





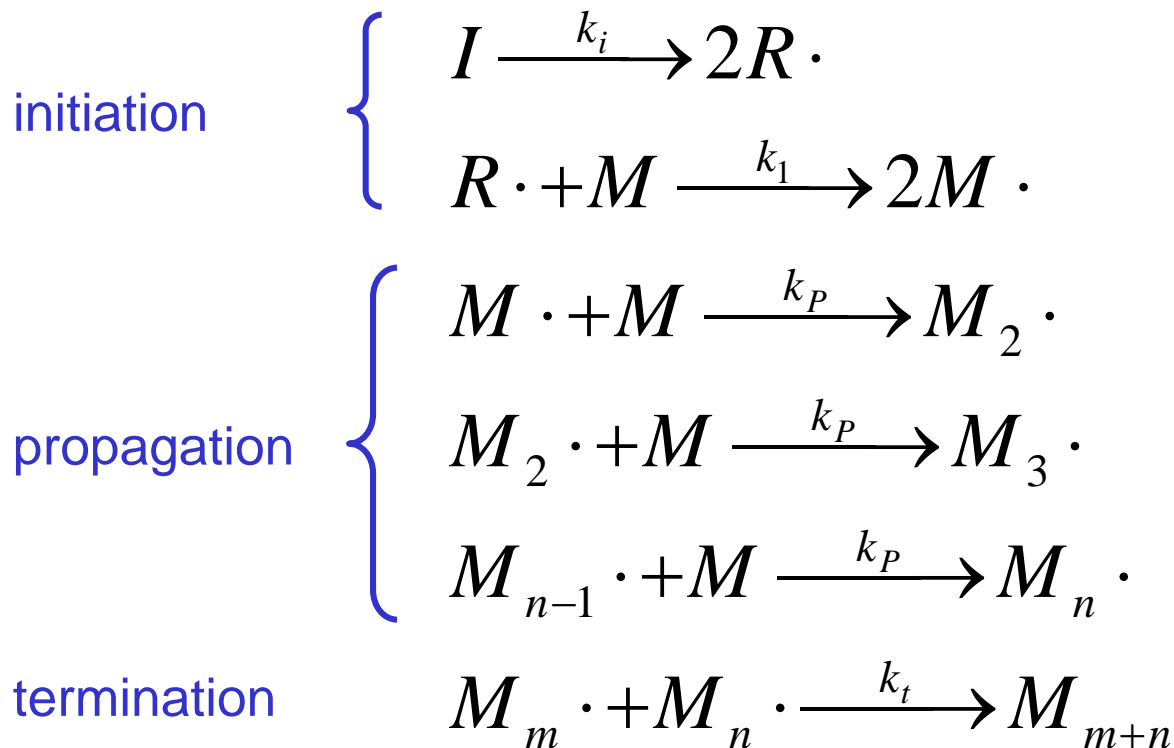
# Free Radical Kinetics: Polymerization

Prof. Attilio Citterio  
Dipartimento CMIC "Giulio Natta"



## Radical Polymerization

Radical polymerization is a reaction in which a polymer chain forms from monomer units, initiated by creation of a monomer radical.

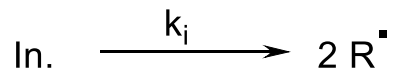


Moad G, Solomon DH. The chemistry of free radical polymerization. London: Pergamon, 1995.



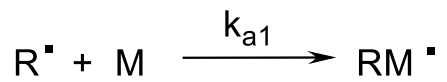
# Free Radical Polymerization Mechanism

Iniziazione

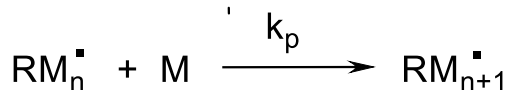
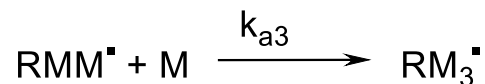
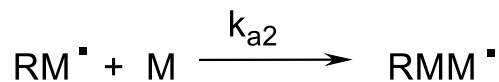


Rifare ISIS

Propagazione

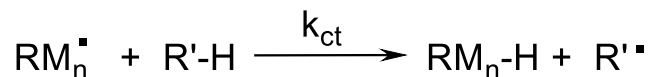


$$\text{Velocità} = k_1[M][R^\bullet]$$

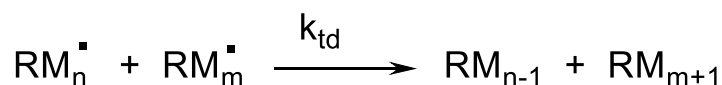
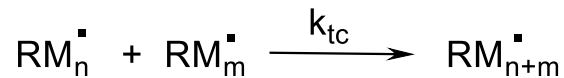


$$\text{Velocità} = k_p[M][RM^\bullet]$$

Trasferimento Catena



Terminazione

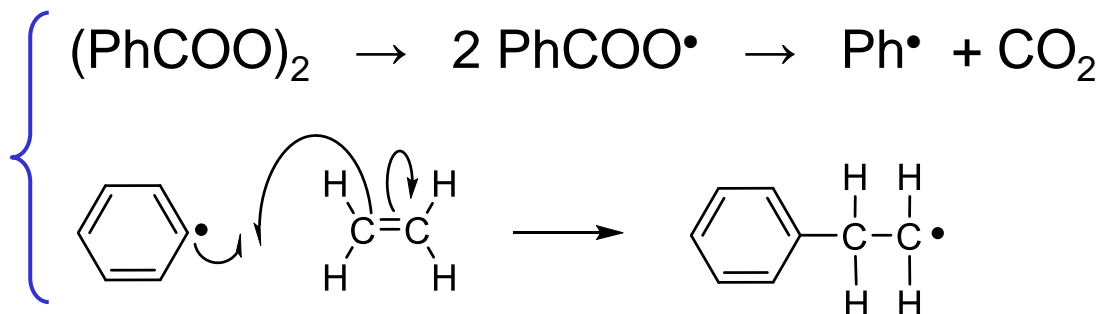


$$\text{velocità} = k_{tc} [RM^\bullet]^2 + k_{td} [RM^\bullet]^2$$

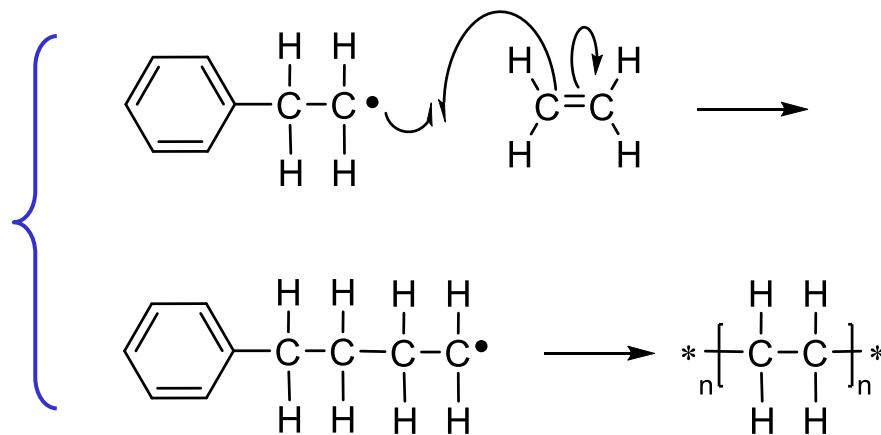


# Initiation and Propagation

Initiation:



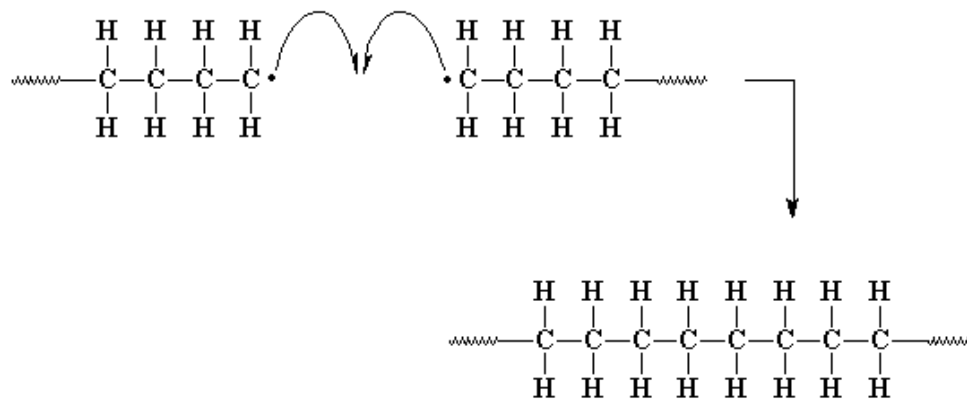
Propagation:



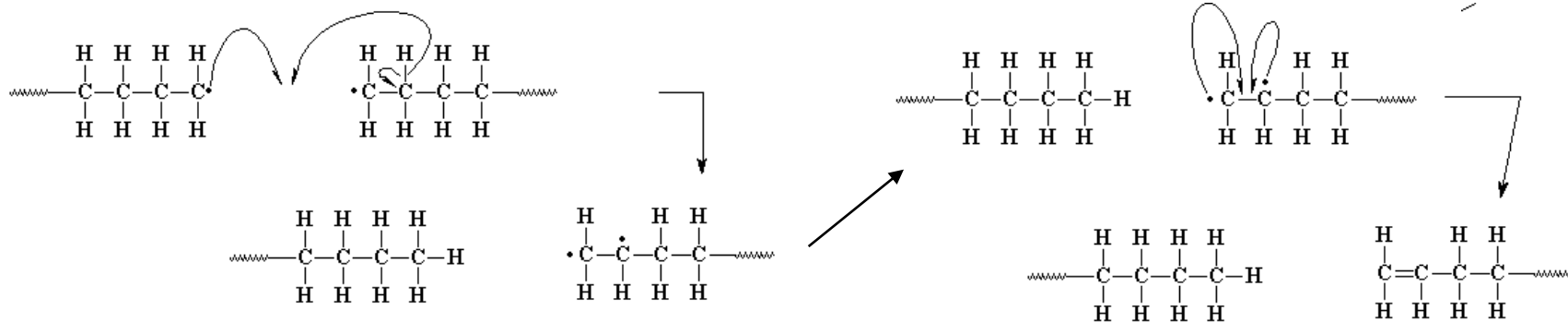


# Termination by Coupling or by Disproportionation

## Termination by coupling



## Termination by disproportionation





## Polymerization Rate Law

$$\frac{d[M]}{dt} = -k_p[M\cdot][M]$$

$$[M\cdot] = [M_1\cdot] + [M_2\cdot] + [M_3\cdot] + \dots$$

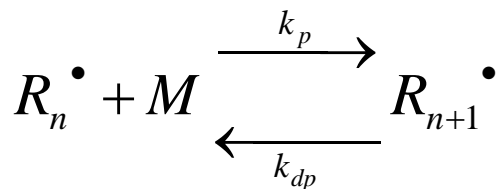
**steady state approximation:**  $[M\cdot] = \left(\frac{\phi k_i}{k_t}\right)^{1/2} [I]^{1/2}$

$$\frac{d[M]}{dt} = -k_p \left(\frac{\phi k_i}{k_t}\right)^{1/2} [I]^{1/2} [M]$$

$\phi$  = probability that  $R^\bullet$  will create a radical chain

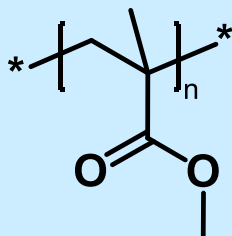


# Ceiling Temperature

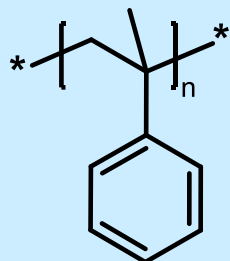


For example:

MMA (pure monomer) 220 °C



$\alpha$ -Methylstyrene (25 °C) = 2.2 mol L<sup>-1</sup>



$$\Delta G = \Delta G^0 + RT \ln K$$

$$= \Delta G^0 + RT \ln \frac{[R_{n+1} \cdot]}{[R_n \cdot][M]}$$

$$\Delta G^0 = RT_c \ln \frac{[R_{n+1} \cdot]}{[R_n \cdot][M]}$$

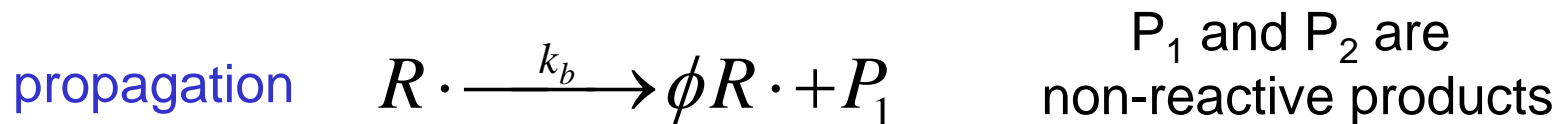
$$\Delta H^0 - T_c \Delta S^0 = RT_c \ln \frac{1}{[M]_c}$$

$$T_c = \frac{\Delta H^0}{\Delta S^0 - R \ln [M]_c}$$



## Branching Reactions

A branching reaction is one in which a single radical species reacts to produce  $\phi$  radical species, where  $\phi \geq 2$  is the **branching efficiency**.



$$[R \cdot] = \frac{\Gamma}{k_{eff}} \left( e^{k_{eff} t} - 1 \right)$$

$$\Gamma = k_i [A][B] \quad \text{and} \quad k_{eff} = k_b (\phi - 1) - k_t$$

$$\lim_{k_t \gg k_b (\phi - 1)} [R \cdot] = \frac{\Gamma}{k_t} \left( 1 - e^{-k_t t} \right) \xrightarrow{t \rightarrow \infty} \frac{\Gamma}{k_t}$$

$$\lim_{k_b (\phi - 1) \gg k_t} [R \cdot] = \frac{\Gamma}{k_b (\phi - 1)} \left( e^{k_b (\phi - 1) t} - 1 \right) \xrightarrow{t \rightarrow \infty} \infty$$





# Kinetics of Free-Radical Polymerization

The process is divided into:

- **Initiation:** Formation of the radicals from catalyst and their first reaction with monomer
- **Propagation:** Subsequent reaction with many monomer units to form a chain
- **Termination:** Loss of the radical by combination of two or reaction with impurity to finish growth of the chain.

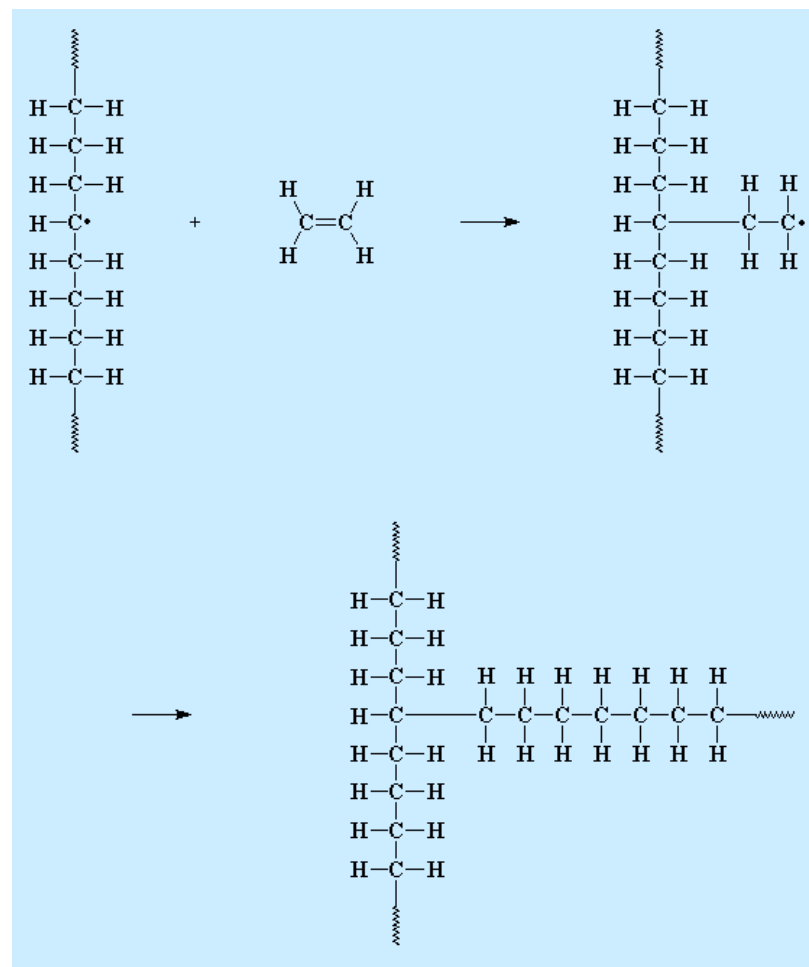
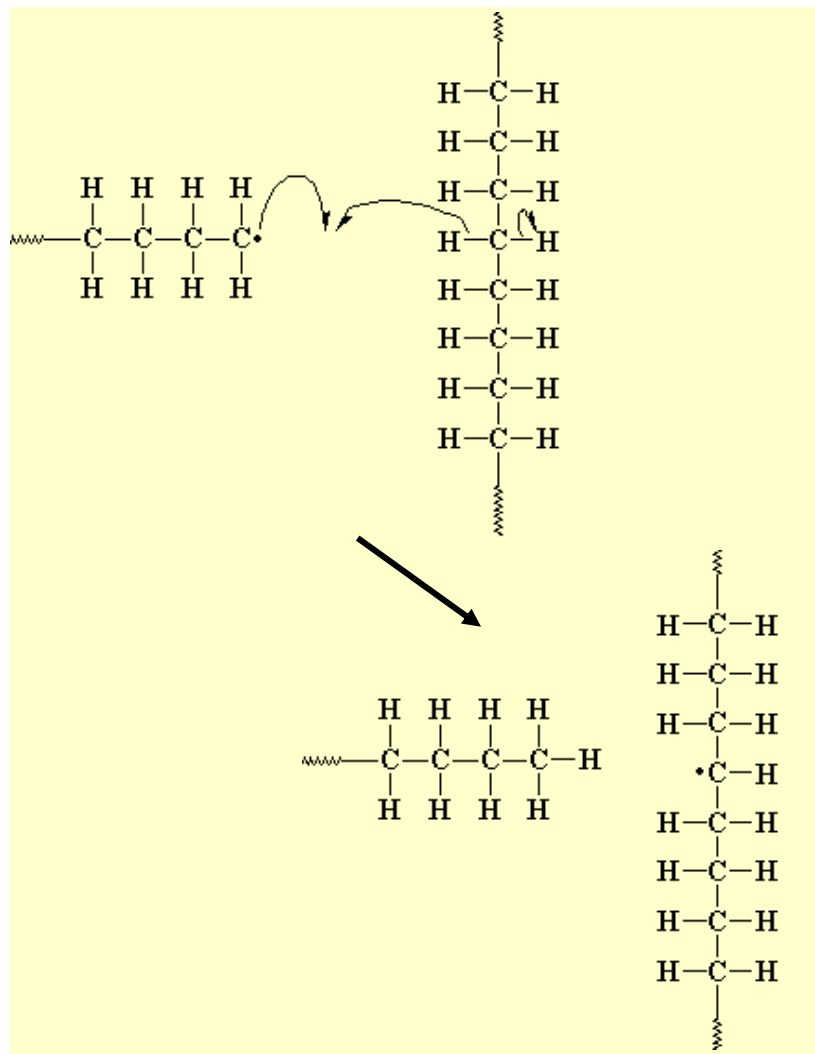
Other important factors are:

- **Inhibition:** Active species, including dissolved oxygen, which rapidly react with and kill radicals. Most monomers contain some inhibitor to stabilize them during shipping.
- **Trommsdorff effect:** Autoacceleration can occur as viscosity increases slow the mobility of the large chains but allow monomers to remain mobile. Propagation continues but termination slows.
- **Chain transfer:** A molecule picks up the radical, terminating a chain but then starts a new chain. Like baton-passing in a relay race, the kinetics is unaffected but the individual chain length is reduced.



# Branching

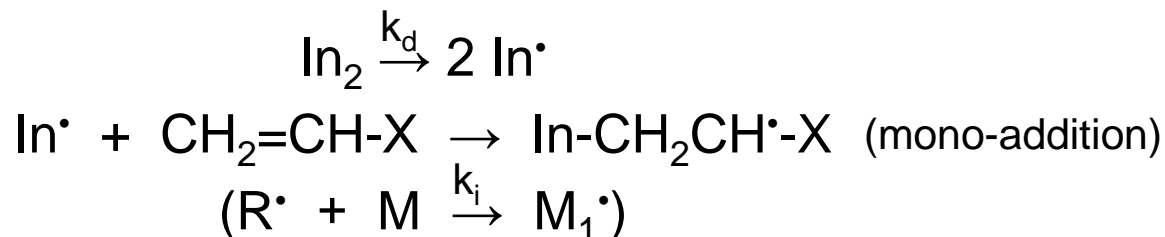
Transfer of the radical center to another molecule and evolution.



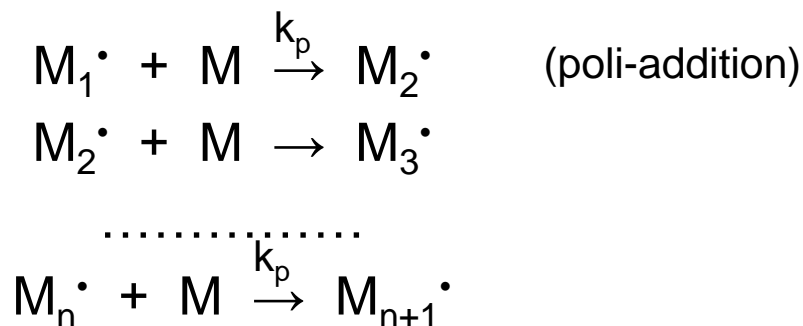


# Mechanism of Free Radical Polymerization

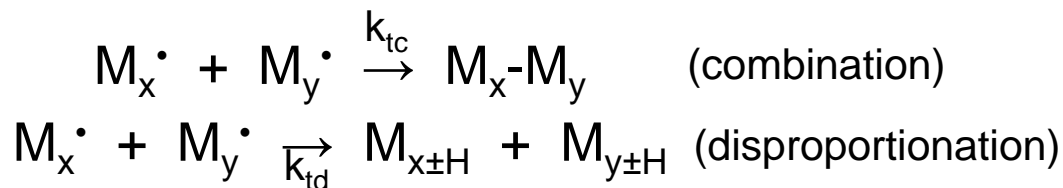
## Initiation:



## Propagation:



## Termination:





# Free Radical Polymerization: Kinetic Aspects

$$r_i = \frac{d[M_i]}{dt} = 2f \cdot k_d [I]$$

$$r_p = -\frac{d[M]}{dt} = k_p [M][M^\bullet]$$

$$r_t = -\frac{d[M^\bullet]}{dt} = 2k_t [M^\bullet][M^\bullet]$$

PROBLEM:

We don't know  $[M^\bullet]$

SOLUTION:

Assume a steady state concentration of transient species

## Steady State Assumption

$$[M^\bullet] = \text{constant}$$

This means that radicals are consumed at the same rate as they are generated

$$r_i = r_t$$

$$2f \cdot k_d [I] = 2k_t [M^\bullet]^2$$

$$[M^\bullet] = \left\{ \frac{f \cdot k_d [I]}{k_t} \right\}^{1/2}$$



# Free Radical Polymerization: Kinetic Aspects – Rate of Propagation

Rate of Propagation = Rate of Polymerization

Normal eqn.:

$$r_p = R_p$$
$$\text{substituting: } r_p = k_p \left[ \frac{f \cdot k_d [I]}{k_t} \right]^{1/2} [M]$$

But  $[I]$  is not constant.:

Extra frill:

$$\text{from } -\frac{d[I]}{dt} = k_d [I] \quad \text{obtain } [I] = [I_0] e^{-k_d t}$$

HENCE

$$R_p = \left\{ k_p \left( \frac{f \cdot k_d}{k_t} \right)^{1/2} \right\} \cdot \left\{ [M] \cdot [I_0]^{1/2} \right\} \cdot \left\{ e^{-k_d \cdot t/2} \right\}$$



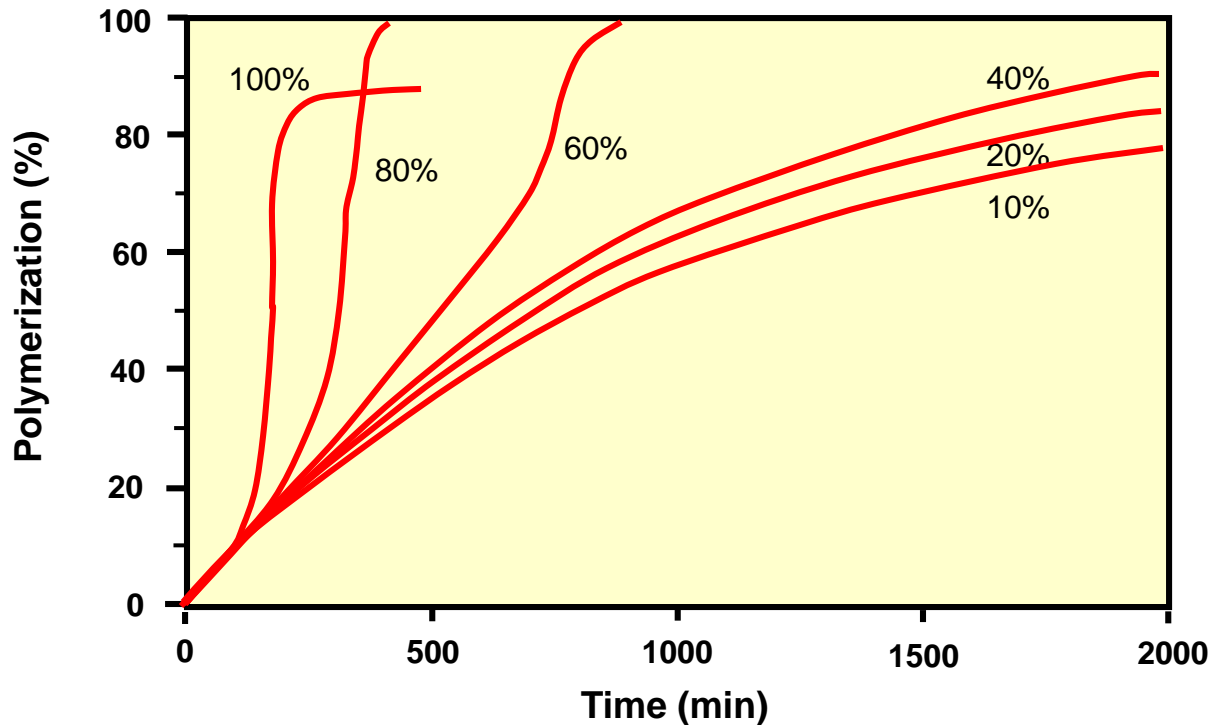
## Partial Conclusions

1. IF WE WANT TO INCREASE  $R_p$   
INCREASE  $[M]$  OR  $[I]$   
BUT, CHANGING  $[I]$  ALSO CHANGES THE MOL. WT. !
2.  $R_p \sim k_p / k_t^{1/2}$   
FOR ETHYLENE AT 130°C AND 1 BAR PRESSURE  
 $k_p / k_t^{1/2} \sim 0.05$   
FOR ETHYLENE AT 200°C AND 2500 BAR PRESSURE  
 $k_p / k_t^{1/2} \sim 3.0$

LDPE is made at high pressure. Propagation increases with P&T but termination doesn't (much).



## Tromsdorff Effect



At high conversion, polymerization takes off as high viscosity slows diffusion of large chains but not monomers and so slows termination but not propagation. This happens when the monomer is concentrated in the starting solution.



## Glass Formation

- In a bulk polymerization, increasing molecular weight will lead to solidification of the resin before all the monomer is consumed.
- If the material is not then annealed above the glass transition, trapped radicals and monomer will slowly react over subsequent years. This can lead to slow shrinkage and, possibly, fracture.
- Most polymers are more dense than the monomer, so shrinkage during polymerization always occurs. The amount of shrinkage is roughly proportional to the fraction of double bonds in the monomer molecule.
- This causes surface roughness in the glass-fiber/unsaturated polyester moldings used for car body parts and debonding in acrylate composite dental fillings. Unsaturated polyester resin is a solution of short polyester chains containing double bonds in styrene.





# Conversion of Monomer

Definition:

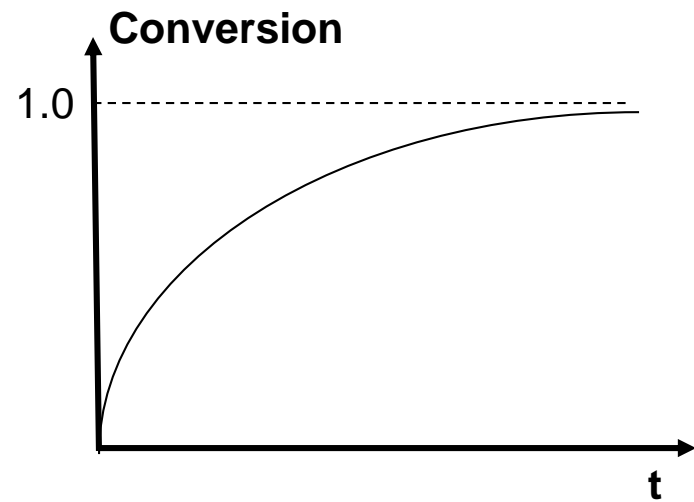
$$\frac{[M_0] - [M]}{[M_0]} = \frac{\text{Amount of monomer used up}}{\text{Amount of monomer at start}}$$

In initial stages of reaction we can assume  $[I] = [I_0] = \text{constant}$

$$\frac{d[M]}{dt} = -k_p \left\{ \frac{f \cdot k_d [I]}{k_t} \right\} [M]$$

integrating

$$\ln \frac{[M]}{[M_0]} = -k_p \left\{ \frac{f \cdot k_d [I_0]}{k_t} \right\}^{1/2} t$$





## Average and Kinetic Chain Length

### Kinetic chain length definition

$$\bar{\nu} = \frac{\text{Rate of monomer addition to growing chains}}{\text{Rate at which chains are started}}$$

This is the average number of monomers polymerized per chain radical at a particular instant of time during the polymerization.

### Average kinetic chain length

$$\bar{\nu} = \frac{\text{\# of monomer reacted}}{\text{\# chains started}}$$

For example, if we have:

1. 100 chains are started
2. 1,000,000 monomers are reacted

In this time period

The average degree of polymerization of these chains is:

$$1,000,000/100 = 10,000$$



## Kinetic Chain Length

There will be some obvious errors (e.g. what about chains that were initiated, but did not terminate just before the start of the chosen period?)

But these decrease as  $t \rightarrow$  small

In the limit of a time period  $dt$

$$\nu = \frac{r_p}{r_i} = \frac{k_p [\text{M}]}{2(f \cdot k_d k_t)^{1/2} [\text{I}]^{1/2}}$$

$$\nu \cong \frac{[\text{M}]}{[\text{I}]^{1/2}} \quad \text{c.f.} \quad r_p \cong [\text{M}] \cdot [\text{I}]^{1/2}$$

The degree of polymerization then depend upon the mechanism of termination:

$$\bar{x}_n = \nu \quad - \text{disproportionation}$$

$$\bar{x}_n = 2\nu \quad - \text{combination}$$



## Instantaneous Number Average Chain Length

What if termination occurs by both mechanisms?

Define an average number of dead chain per termination reaction:

$$\xi = \frac{\text{Rate of dead chain formation}}{\text{Rate of termination}} = \frac{(2k_{td} + k_{tc}) \cdot [M^\bullet]^2}{(k_{td} + k_{tc}) \cdot [M^\bullet]^2} = \frac{(2k_{td} + k_{tc})}{k_t}$$

Hence

$$\bar{x}_n = \frac{k_p [M^\bullet] \cdot [M]}{(2k_{td} + k_{tc}) \cdot [M^\bullet]^2} \quad \bar{x}_n = \frac{k_p [M]}{\xi (f \cdot k_d \cdot k_t)^{1/2} \cdot [I]^{1/2}}$$

Notice that molecular weight can be increased:

- by reducing the initiator, but this slows the reaction,
- or by increasing the monomer concentration but this leads to a Tromsdorff effect.

Free radical molecular weight distributions tend to be very broad ( $M_w/M_n=20$ ) because rates change with extent of reaction (Condensation  $\sim 2$  ; Anionic 1-1.2 “Poisson dist.”)



## Heat of Polymerization of Common Olefins

Monomer	$\Delta H_p(\text{kJ}\cdot\text{mol}^{-1})^*$
Ethylene	94.9
Propylene	85.7
Isobutene	51.4
1,3-Butadiene	72.7
Isoprene	74.4
Styrene	69.8
$\alpha$ -Methylstyrene	35.1
Vinyl chloride	95.7
vinyliden chloride	155.5
tetrafluoroethylene	155.5
Methyl acrylate	78.6
Methyl methacrylate	56.4
Vinyl acetate	87.8

\*with reference to the conversion of liquid monomer to amorphous or slightly crystalline polymer

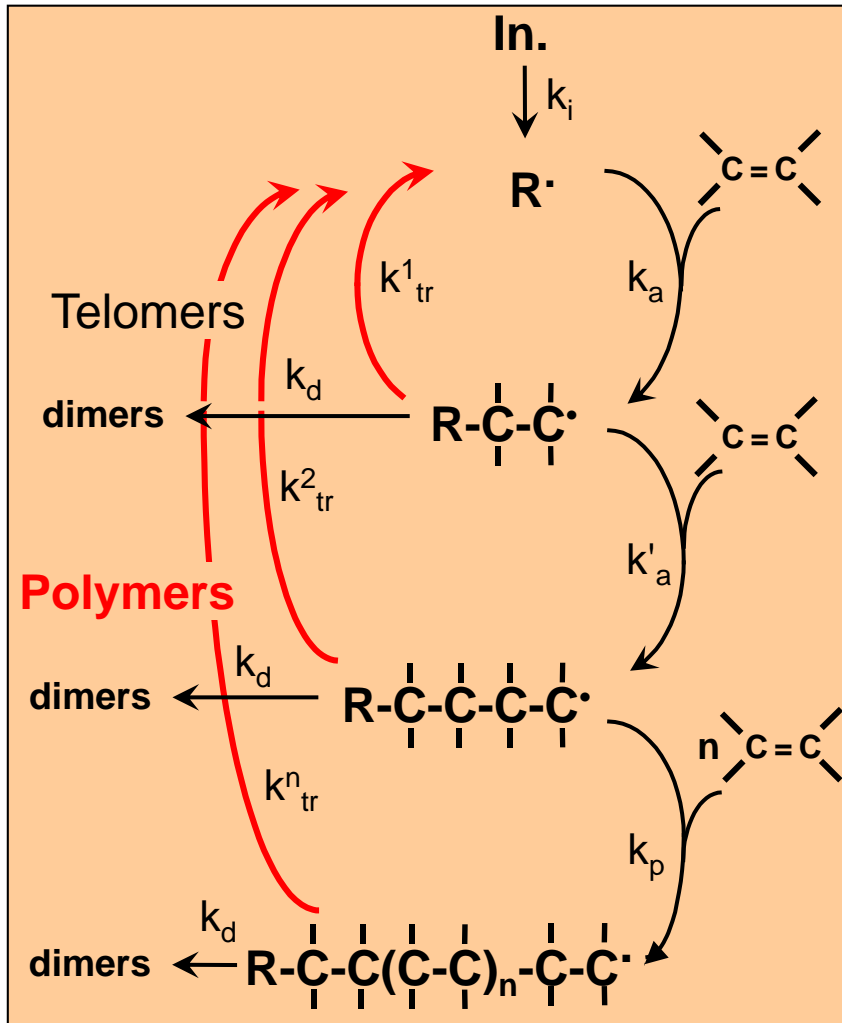
# Propagation Rate Constants in Radical Polymerization

Monomer	$K_p$ ( $M^{-1}\cdot s^{-1}$ ) (60°)	log A ( $M^{-1}\cdot s^{-1}$ )	E (kcal·mole <sup>-1</sup> )
Acrylamide	18.000 <sup>a</sup>	-	-
Vinyl chloride	12.300	6.5	3.7
N,N-Dimethylacrylamide	11.000 <sup>b</sup>	-	-
Vinyl acetate	3.700	8.4	7.3
Methyl acrylate	2.090	8.0	7.1
Acrylonitrile	1.960	-	-
Methyl Methacrylate	734	7.0	6.3
Styrene <sup>c</sup>	145	6.7	7.3
Butadiene	100	8.1	9.3
Isoprene	50	8.1	9.8

<sup>a</sup> at 25°C. <sup>b</sup> at 50°C. <sup>c</sup> Also reported  $k$  (60°)= 176; logA = 7.0, e E =32.6.



# Chain Transfer Processes



**Chain transfer:** interception of propagating radical by different agents: solvent, monomer, added species.

Chain transfer constant:

$$C = k_{tr}/k_p$$

$$C_I = k_{trI}/k_p; C_S = k_{trS}/k_p; C_M = k_{trM}/k_p$$

The value of chain transfer constant is deduced from a Mayo plot:

$$\frac{1}{DP} - \frac{1}{DP_0} = C_s \frac{[I]}{[M]}$$



# Determination of Chain Transfer Rate Constants

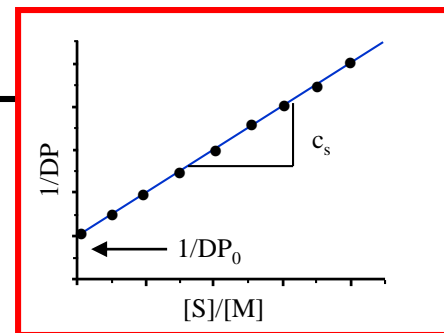
Mayo equation:

$$\frac{1}{DP_n} = \frac{1}{DP_n^0} + C_s \frac{[\text{Transfer Agent}]}{[\text{Monomer}]}$$

$DP_n$  = polymerization degree WITH the transfer agent

$DP_n^0$  = polymerization degree WITHOUT the transfer agent

$C_s$  = Chain Transfer Rate Constant



Chain transfer agents are used to keep MW down.

- Hydrogen in Ziegler polymers
- Mercaptans in free radical reactions





# Chain Transfer: Kinetics Consideration



$$-\frac{d[\text{M}^\bullet]}{dt} = -2k_{td} [\text{M}^\bullet]^2 + k_{tc} [\text{M}^\bullet]^2 + 2k_{tr} [\text{T}] \cdot [\text{M}^\bullet]$$

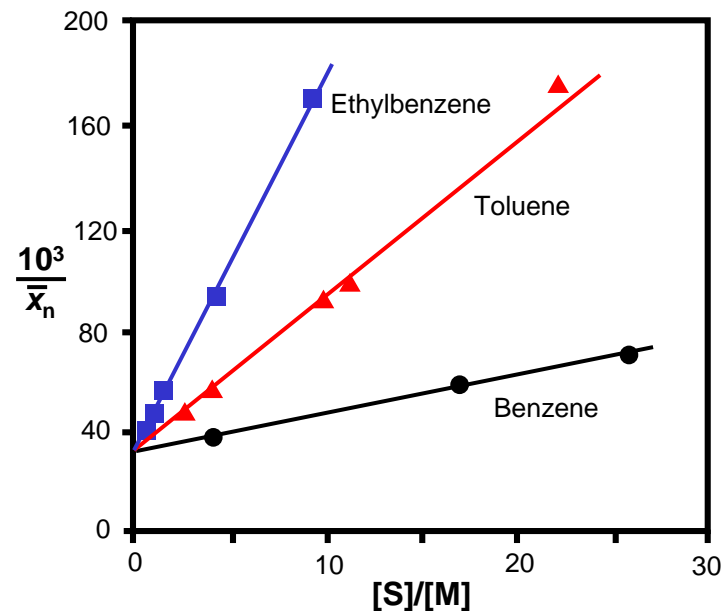
Can then obtain

$$\bar{x}_n = \frac{k_p [\text{M}]}{\xi (f \cdot k_d + k_t)^{1/2} [\text{I}]^{1/2} + k_{tr} [\text{T}]}$$

or

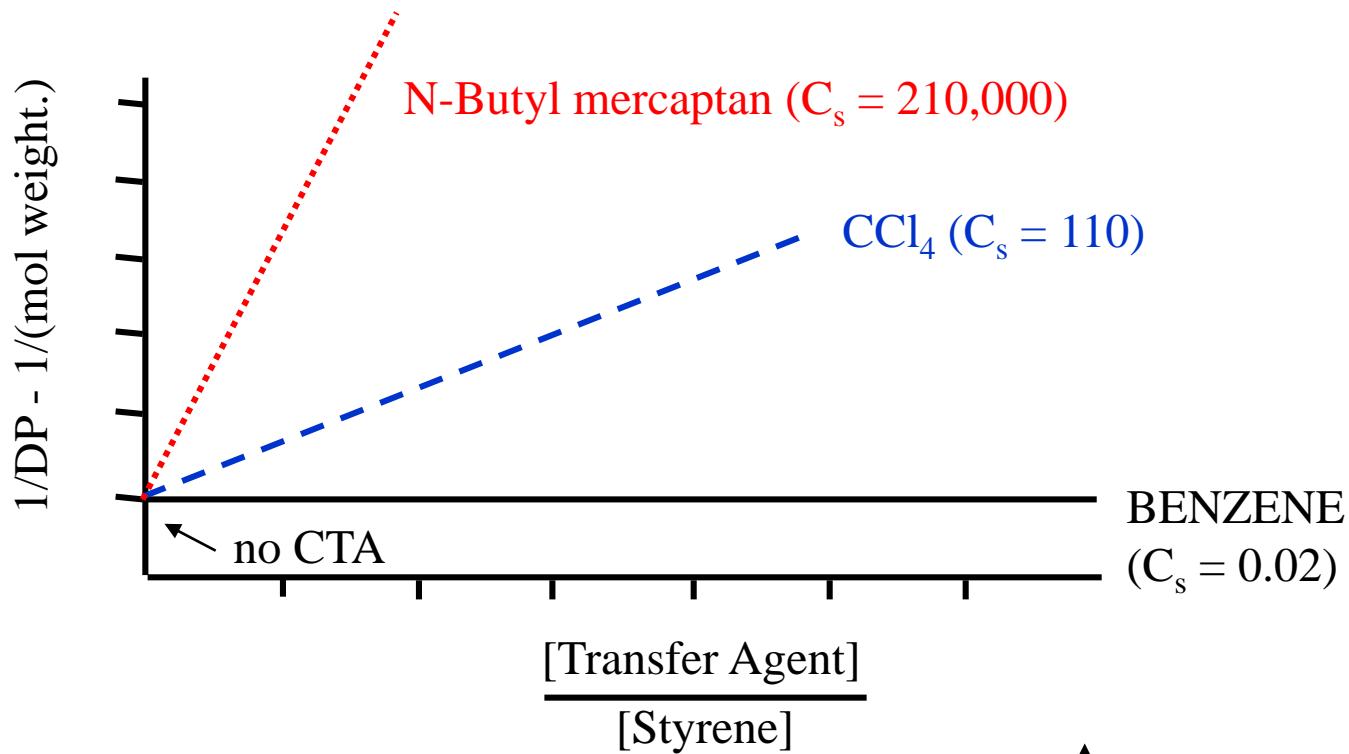
$$\frac{1}{\bar{x}_n} = \frac{1}{(\bar{x}_n)_0} + \frac{C \cdot [\text{T}]}{[\text{M}]} \quad \text{where} \quad C = k_{tr}/k_p$$

$$\bar{x}_n = DP_n$$

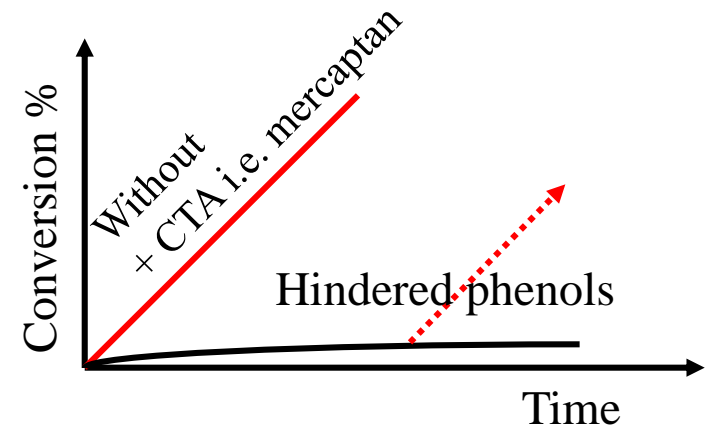




# Effect of CTA on the Polymerization Degree of Styrene

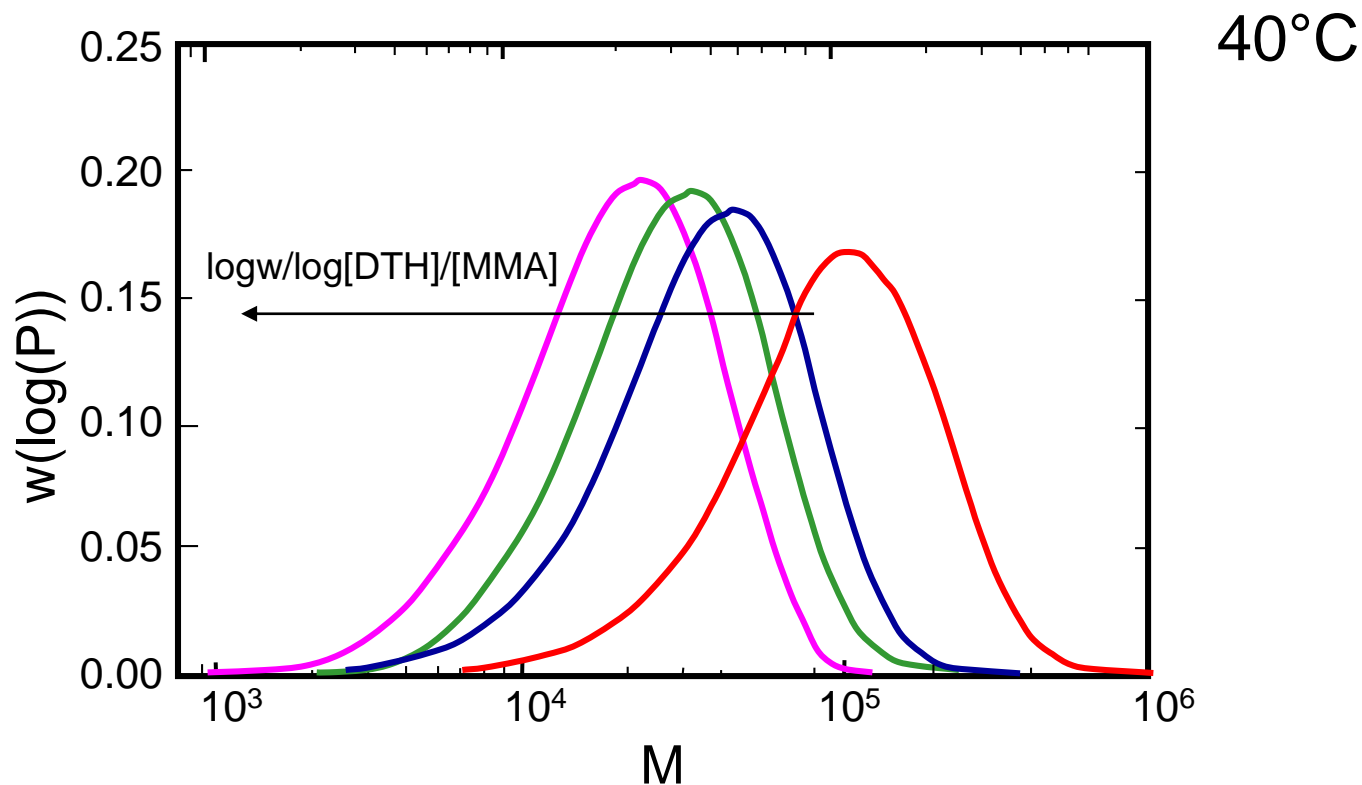


**CTA behave differently from inhibitors!**





# Molecular Weight Distribution on Monomer/CTA Ratio (MMA/C<sub>12</sub>H<sub>25</sub>SH)





# Living and Controlled Polymerisations

Controlled or 'Living' free-radical polymerizations are based on two principles: reversible termination or reversible transfer.

## ❖ Living systems

- constant number of polymer chains
- no permanent chain stopping reactions
- dormant and active state
- control of chain-growth
- narrow MWD (Poisson)
- $\langle M_n \rangle$  vs. monomer conversion is linear

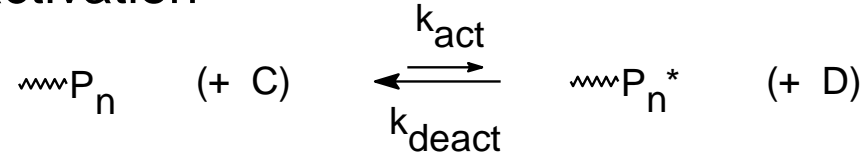
## ❖ Controlled systems

- side reactions do occur
  - however still control of end groups, topology, monomer sequencing

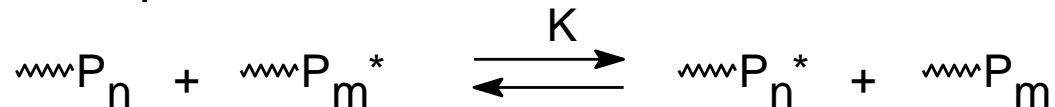


# How to Realise a Living System

- Reversible activation



- Chain transfer processes



- Combination of both

- Reversible homolytic cleavage

- Nitroxide-Mediated LRP
- Transition Metal Mediated LRP

- Chain transfer processes

- Addition Fragmentation
- RAFT
- Catalytic Chain Transfer Polymerisation

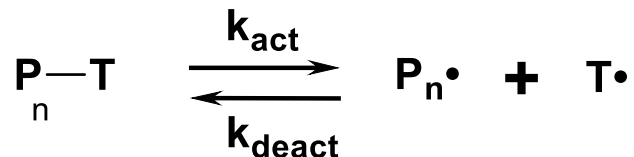
- Combination of both

- Iniferters

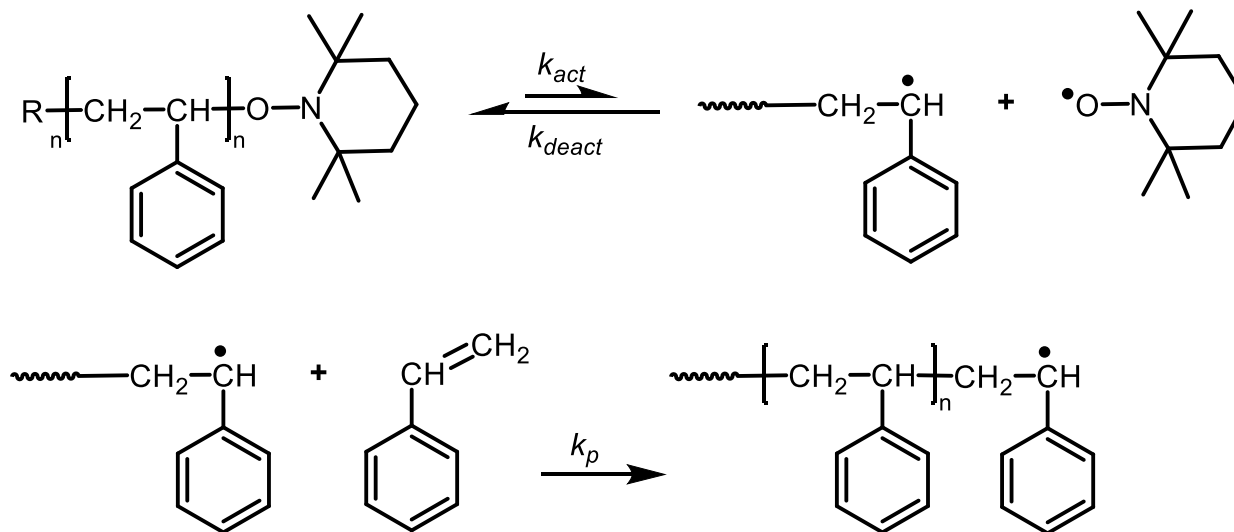




# Reversible Activation of Dormant Polymer Chains (NMCRP).



Dissociation of a typical alkoxyamine into a carbon-centered radical (ethylbenzene radical) and a nitroxide (TEMPO).



Solomon DH, Rizzardo E, Cacioli P. **1986**; US patent 4,581429.  
Hawker CG, Bosman AW, Harth E. *Chem. Rev.* **2001**, 101, 3661.



## Mechanism of Nitroxide-Mediated CRP.

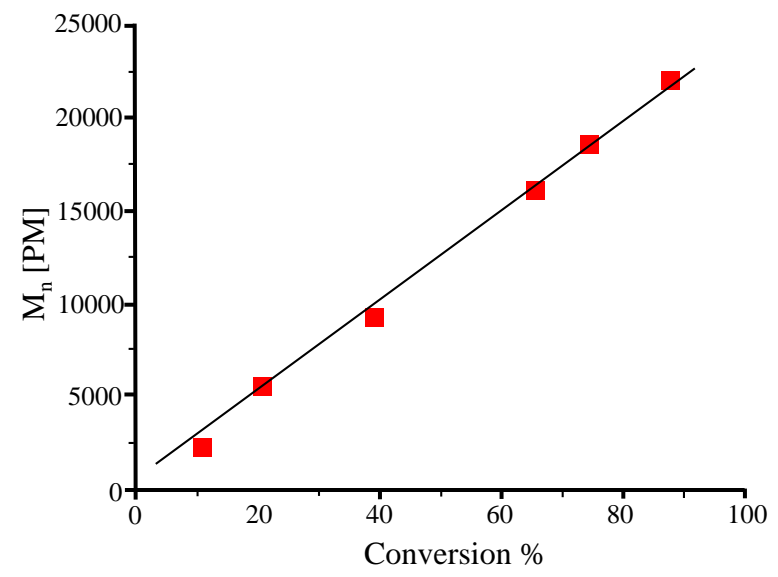
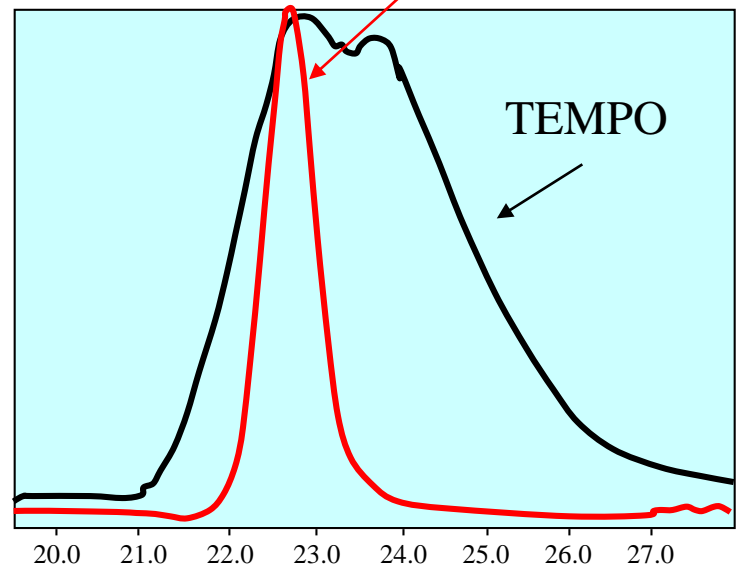
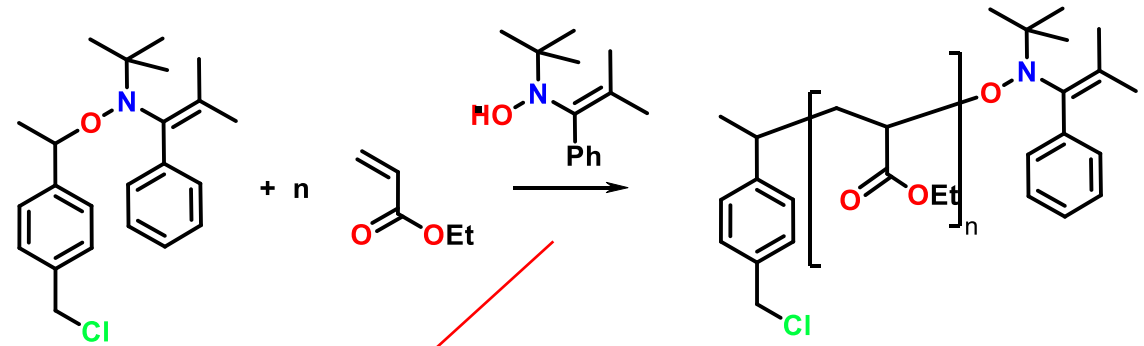
R-T represents an alkoxyamine, T• represents a nitroxide.







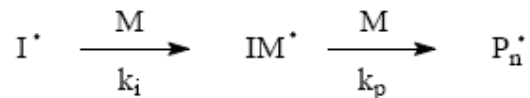
# CRP Polymerization: Nitroxide Structure



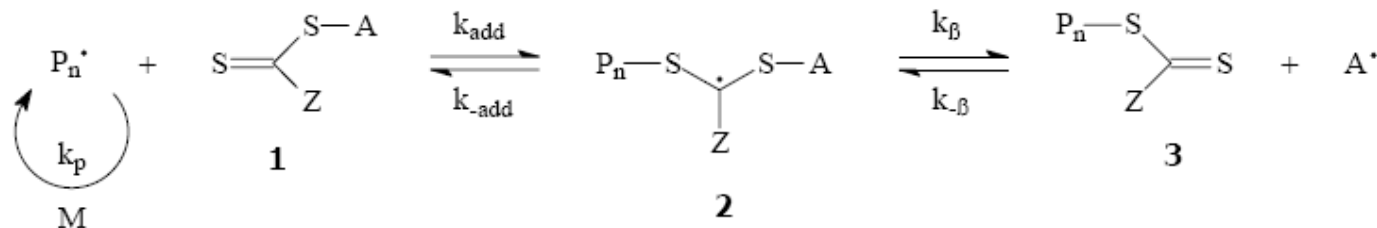


# Reversible Addition-Fragmentation chain Transfer (RAFT) process

Initiation



(a) Chain transfer



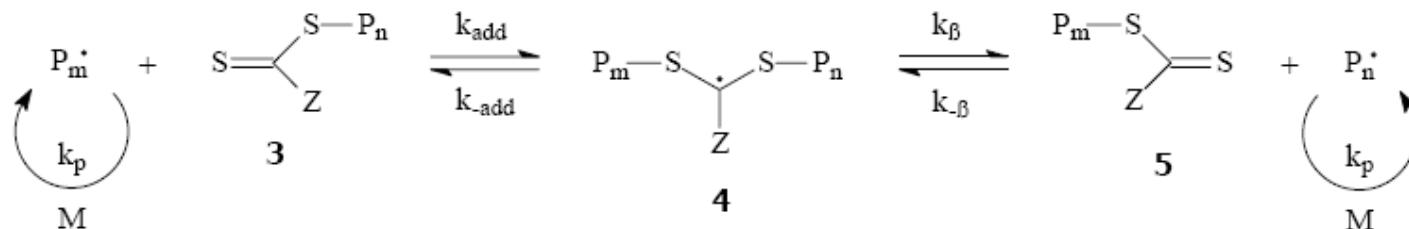
(b) Reinitiation



$$\bar{M}_n = FW_{\text{RAFT}} + \frac{[M]_0 \cdot FW_{\text{mon}} \cdot X}{[\text{RAFT}]_0 + df([I]_0 - [I]_t)}$$

X = Monomer conversion

(c) Chain equilibration



Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, 31, 5559-5562.



## Schematic representation of the proposed RAFT mechanism.

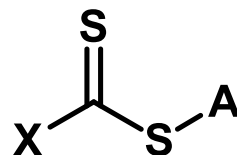
It should be noted that all reactions are equilibria, and that in these equilibria any radical can react with any dormant species/RAFT agent.

- a) Addition of a polymeric, initiator derived radical to the initial transfer agent **1**, forming intermediate radical **2**. The intermediate radical can either fragment into the two species it was composed from, or into dormant species **3** and a small, expelled radical  $A\bullet$ .
- b) Reinitiation of the polymerization by addition of the expelled radical  $A\bullet$  to monomer, rather than back reaction with **3** forming **1**. For this assumption to hold,  $A\bullet$  must be a good leaving group capable of reinitiating polymerization, so  $k_i[M][A\bullet] \gg k_{-1}[3][A\bullet]$
- c) Equilibrium between active propagating chains and dormant chains **3** and **5** through intermediate radical **4**.

Barner-Kowollik C, Davis TP, Heuts JPA, Stenzel MH, Vana P, Whittaker M.  
*J. Polym. Sci. Polym. Chem.* **2003**, *A41*, 365.



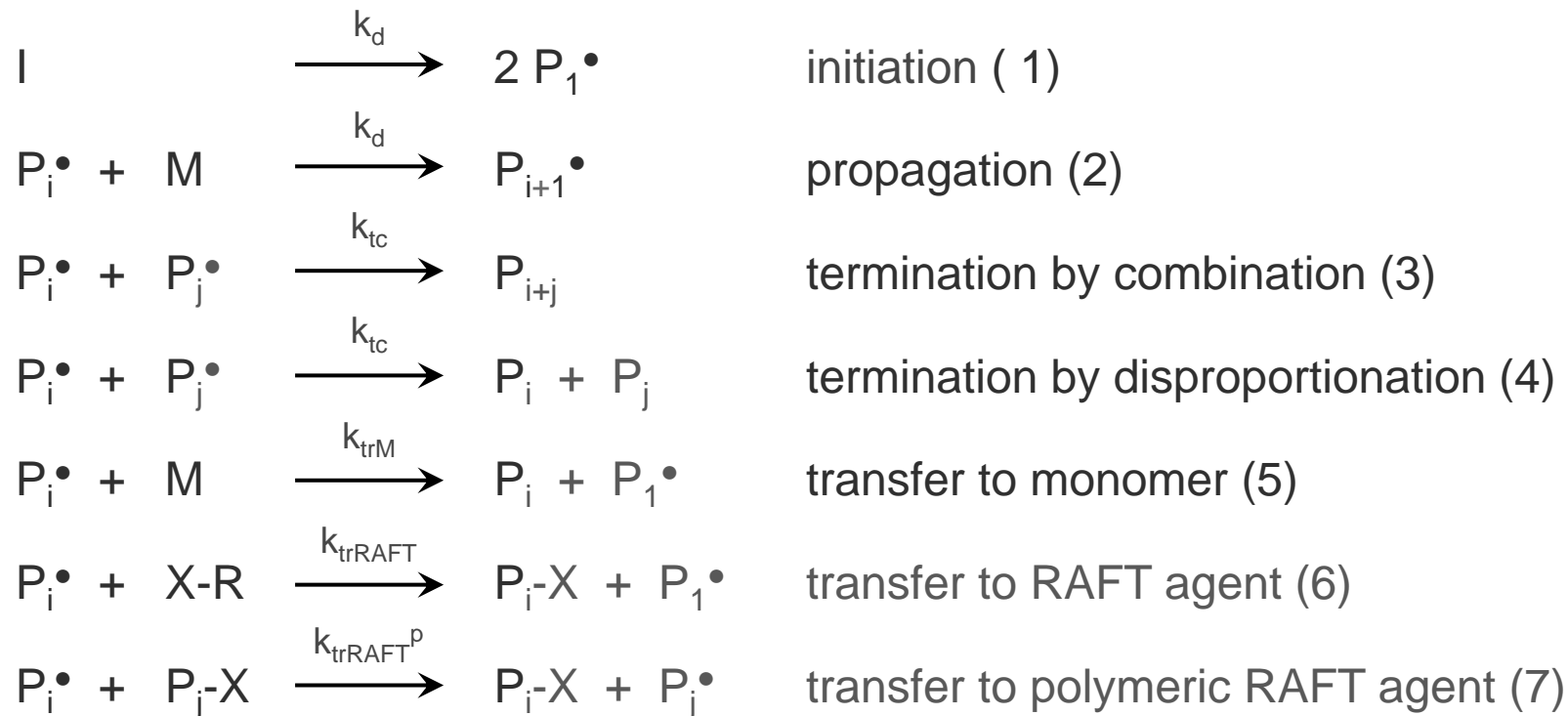
## The Various RAFT Moieties



RAFT agent type	X	A
dithioester	Alkyl-, aryl	Usually a tertiary alkyl moiety substituted with an electron-withdrawing group
xanthate	Alkyl-O-	
trithiocarbonate	Alkyl-S-	
dithiocarbamate		



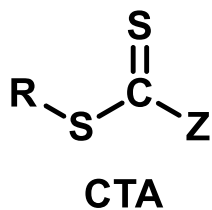
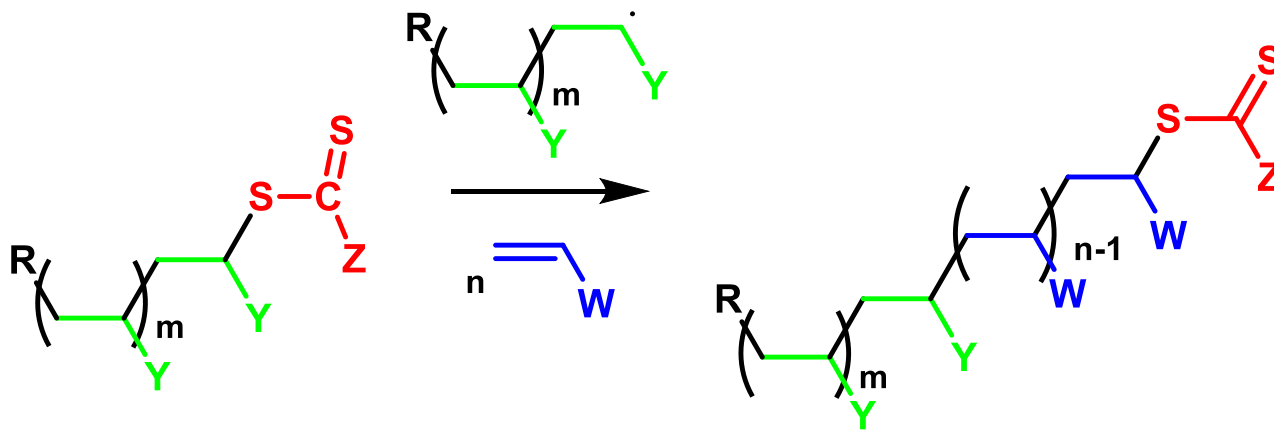
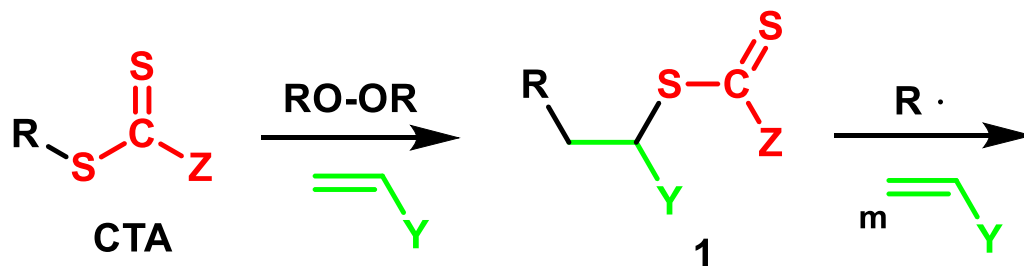
# Kinetic scheme of a bulk polymerization in the presence of a RAFT agent



I is the initiator,  $P_i^\bullet$  is a radical with degree of polymerization  $i$ , M is the monomer,  $P_i$  a dead chain with degree of polymerization  $i$ , X-R the RAFT agent and  $P_i-X$  a dormant chain with degree of polymerization  $i$ .



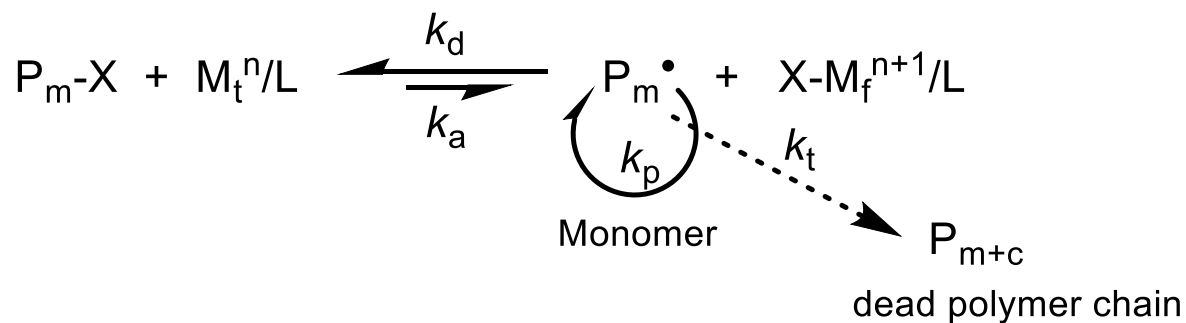
# Chain Transfer Agent (CTA)



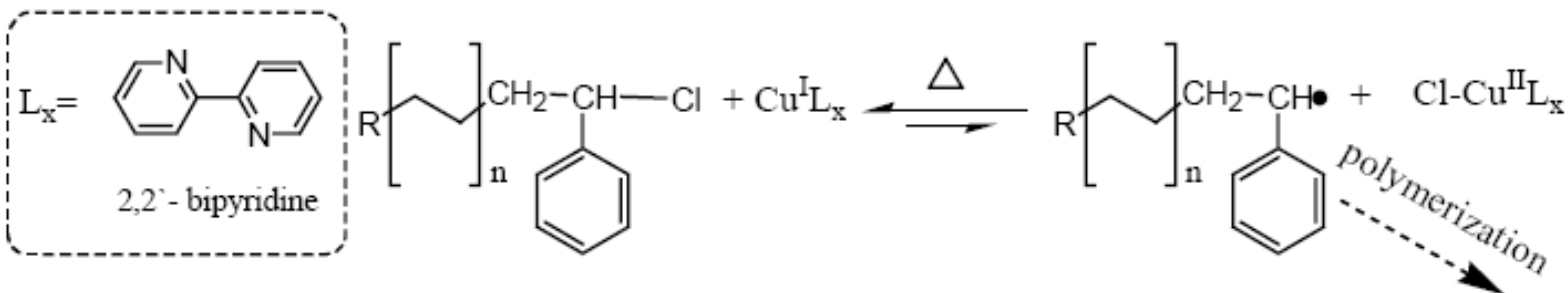
where, R = C-centered radical  
Z = OCH<sub>2</sub>CH<sub>3</sub> for MADIX  
CH<sub>3</sub> or C<sub>6</sub>H<sub>5</sub> for RAFT

# Atom Transfer Radical Polymerization (ATRP)

A)  $k_a$  = activation  
 $k_d$  = deactivation



B)

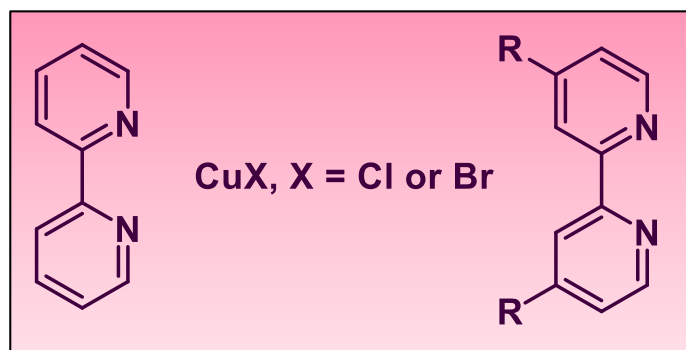


Wang J-S, Matyjaszewski K. *J. Am. Chem. Soc.* **1995**, *117*, 5614.  
 Kamigaito M, Ando T, Sawamoto M. *Chem. Rev.* **2001**, *101*, 3689.



# Transition Metal Mediated Radical Polymerisation

Matyjasewski, JACS (1995), p5614



Sawamoto, Macromolecules, p1721

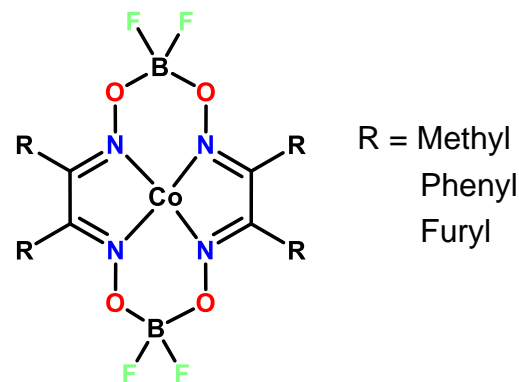
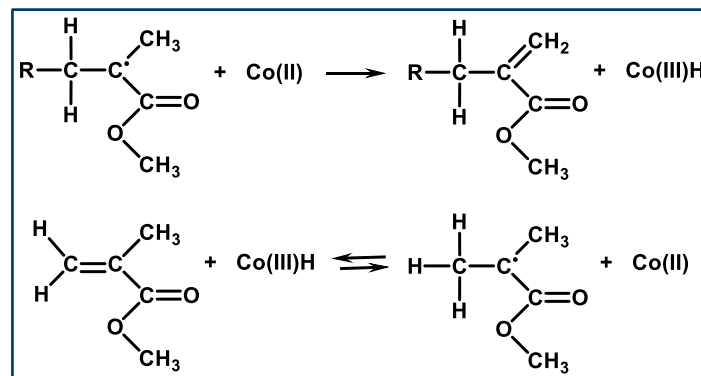
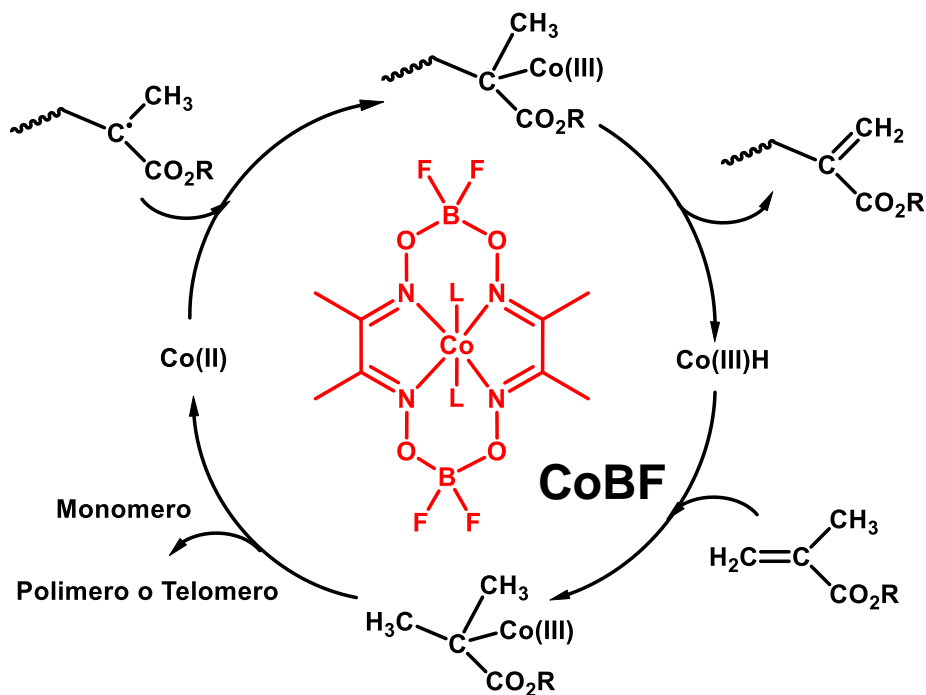






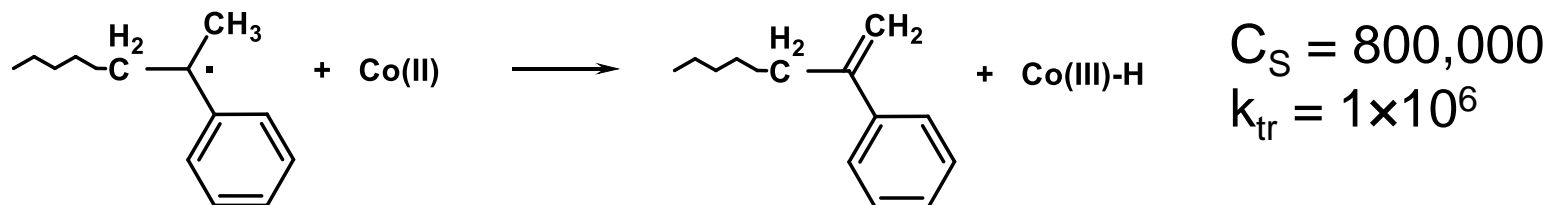
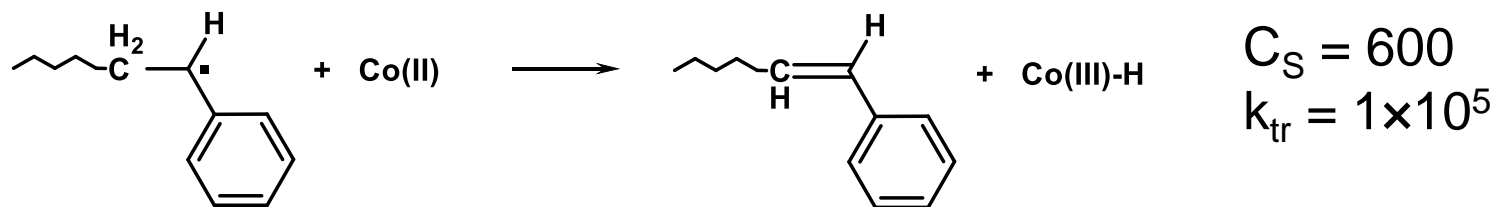
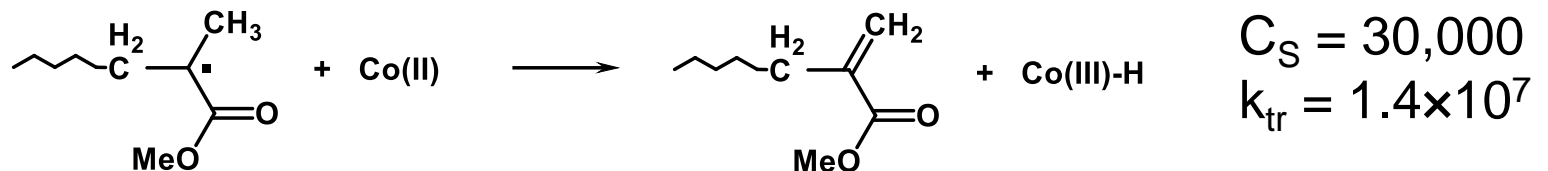
# Catalytic Chain Transfer Polymerization (CCTP)

- Certain Low-Spin Cobalt Complexes
- Typical [Mon]/[Co] ratio of ca.  $10^6$





## CCT with Different Monomers



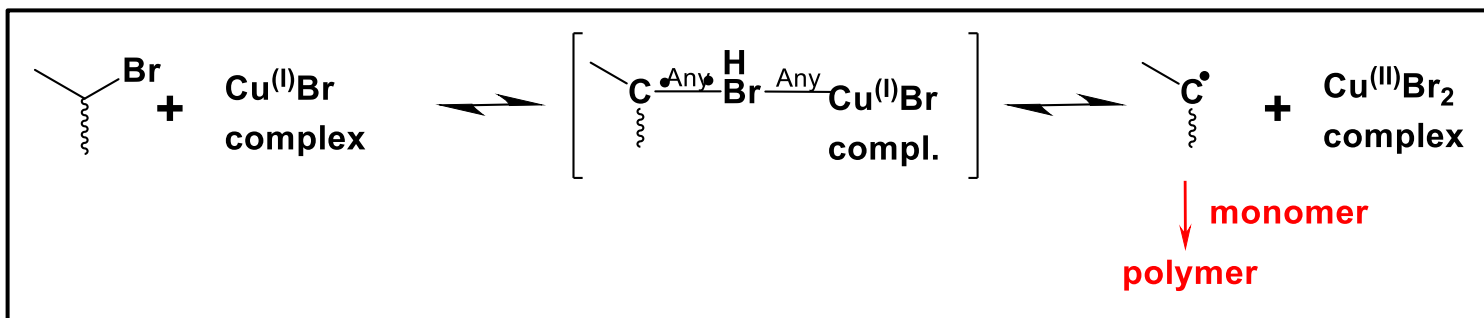
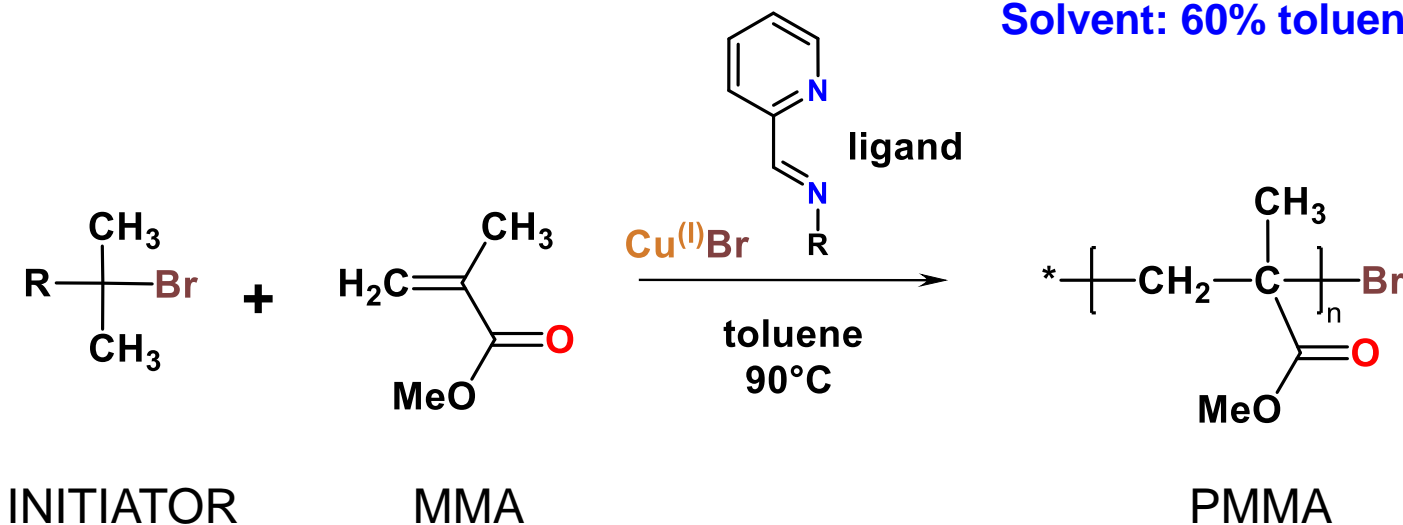
T.P. Davis, H. Heuts, *Macromolecules*, 1999



# CCT Polymerization of MMA by Cu catalyst

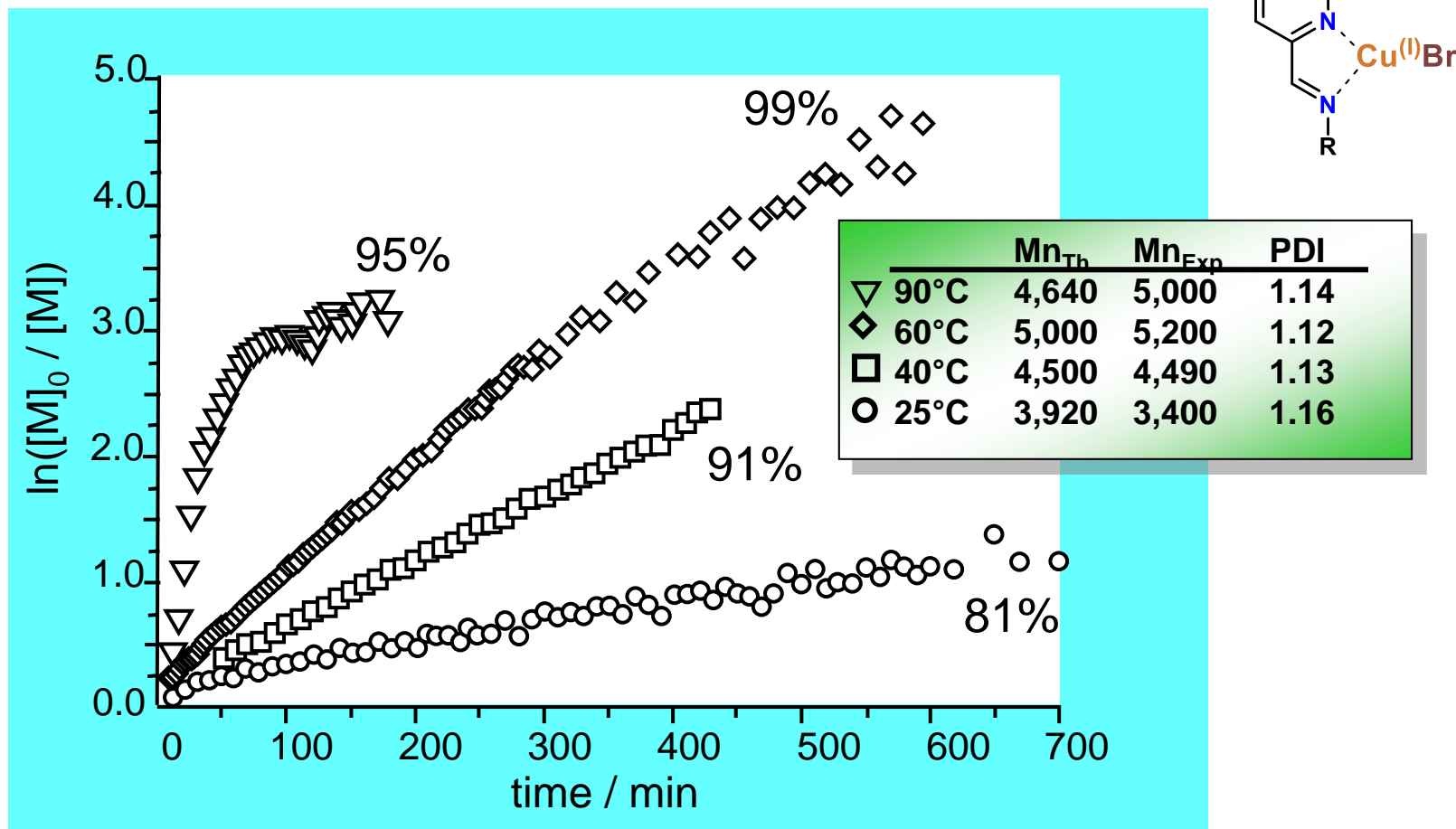
## Polymerization System

Initiator / CuBr / ligand = 1:1:2  
Solvent: 60% toluene





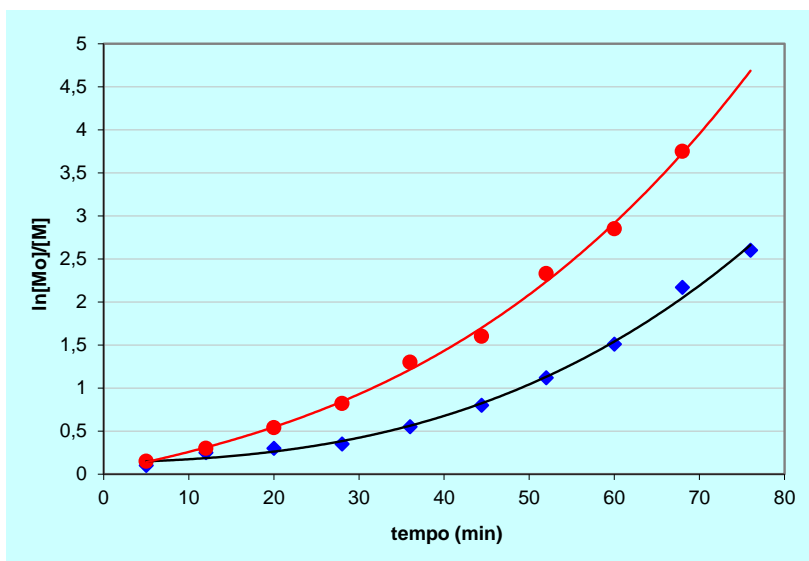
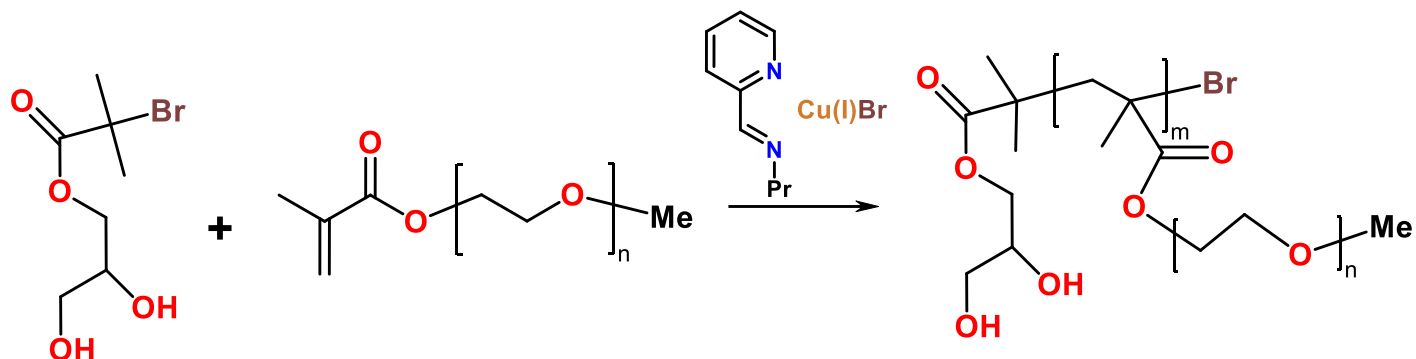
# CCT Polymerization Kinetics of Styrene



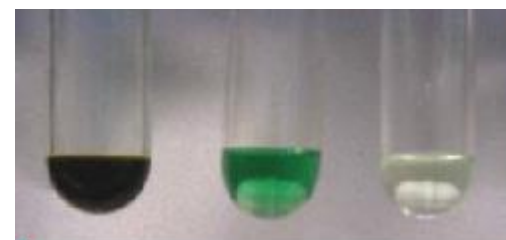
<http://www.warwick.ac.uk/polymers>



# CCT Water Polymerization at 25 °C



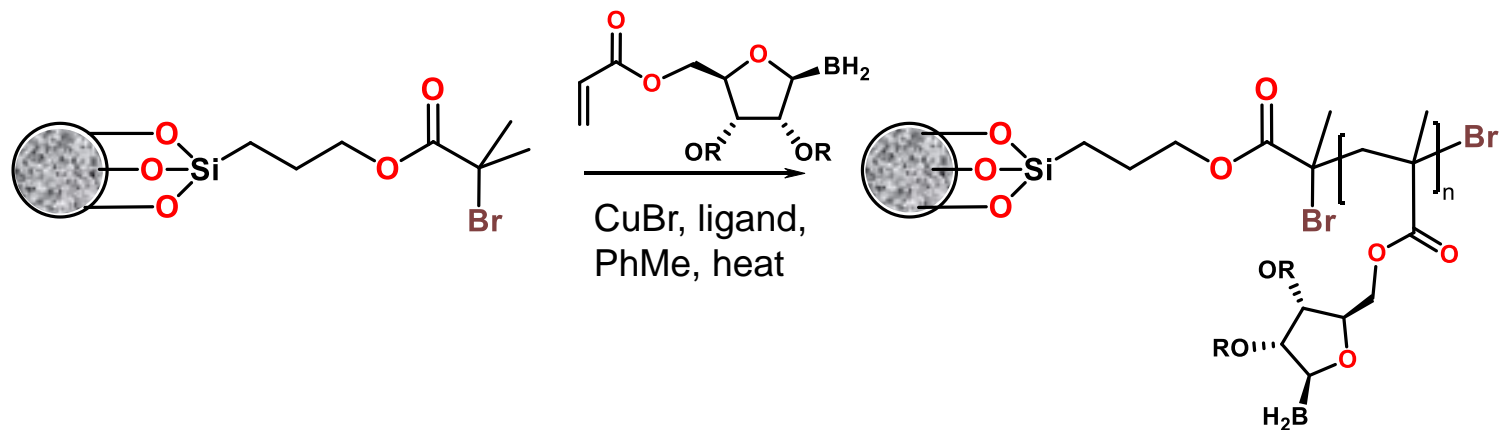
Kinetic at 25°C (•) and at 35°C (◆)  
 $M/I/Cu(I)/Cu(II)/L = 10/1/0.5/0.5/3$



Cu/I: 1/1      1/20      1/100



# Silica Gel Supported Polymers

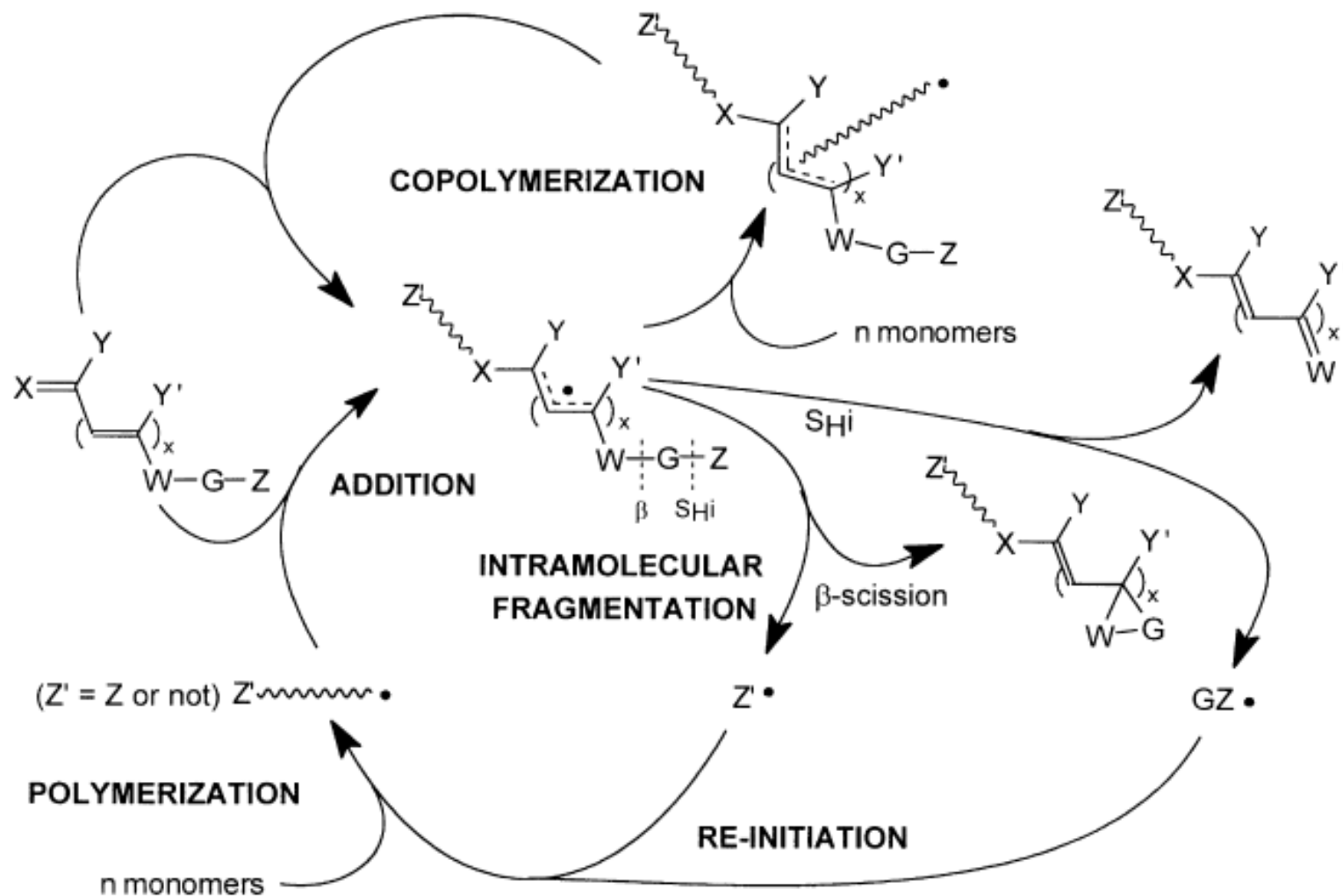


Monomer	Ligand	Load (mmol/g)	Initiator Weight growth (%)
<b>7</b>	NPMI	1.51	188
<b>8</b>	NPMI	1.11	117
<b>7 / 8</b>	NPMI	1.04	105

A. Marsh, A. Khan, M. Garcia, D. M. Haddleton *Chem. Commun.* **2000**, 2083



# Mechanism of AFCT free radical polymerization, through $\beta$ -scission or homolytic substitution.



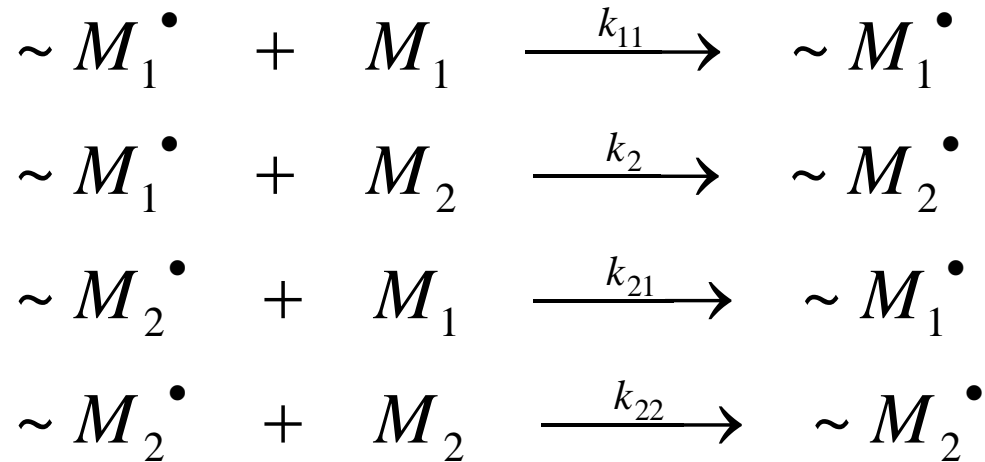






# Radical Copolymerization

- Terminal or Ultimate model



- Reactivity ratio's

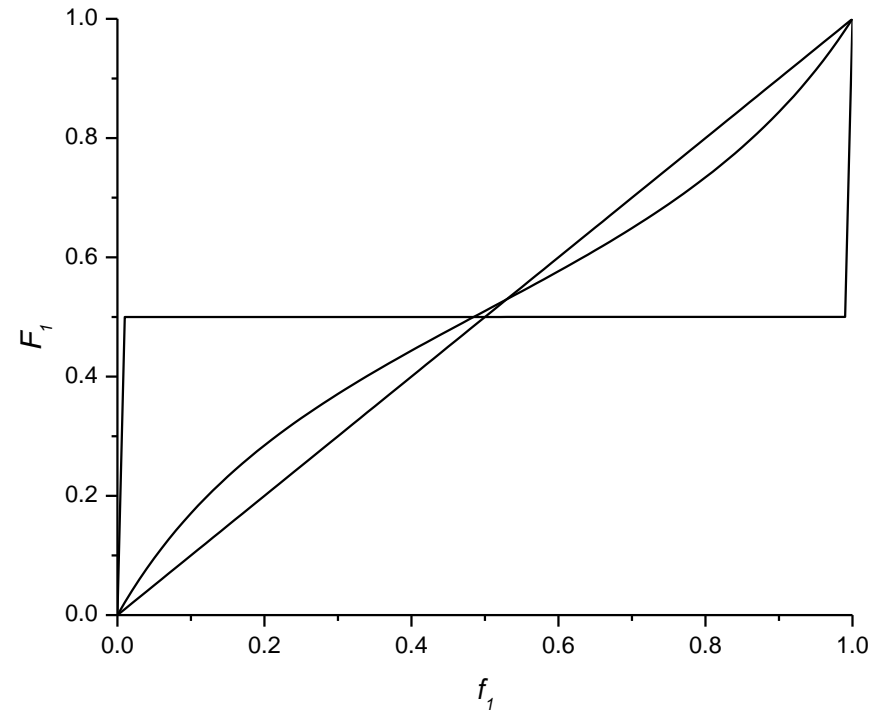
$$r_i = \frac{k_{ii}}{k_{ij}}$$

Where i and j are 1 or 2,  
and  $i \neq j$



# Intrinsic Copolymerisation Equation

$$F_1 = \frac{r_1 f_1^2 + f_1 f_2}{r_1 f_1^2 + 2 f_1 f_2 + r_2 f_2^2}$$



Integrated Copolymerisation Equation:

$$X = 1 - \left( \frac{f_1}{f_{1,0}} \right)^\alpha \left( \frac{f_2}{f_{2,0}} \right)^\beta \left( \frac{f_{1,0} - \delta}{f_1 - \delta} \right)^\gamma$$

$$\alpha = \frac{r_2}{1 - r_2} \quad \beta = \frac{r_1}{1 - r_1} \quad \delta = \frac{1 - r_1 r_2}{(1 - r_1)(1 - r_2)} \quad \gamma = \frac{1 - r_2}{2 - r_1 - r_2}$$



## Conditional Probabilities in TM

- Conditional probabilities are used to describe copolymer composition and the monomer sequence distribution

$$p_{12} = \frac{1}{1 + r_1 \frac{f_1}{f_2}} \quad p_{21} = \frac{1}{1 + r_2 \frac{f_2}{f_1}}$$

***Composition:***

$$\frac{F_1}{F_2} = \frac{p_{21}}{p_{12}}$$

***Sequence Distribution:***

$$\begin{aligned} F_{111} &= (1 - p_{12})^2 \\ F_{112} + F_{211} &= 2 p_{12} (1 - p_{12}) \\ F_{212} &= p_{12}^2 \end{aligned}$$



## Penultimate Model

- now 4 reactivity ratio's are defined

$$r_{ij} = \frac{k_{ijj}}{k_{ijk}} \quad \text{Where } i, j \text{ and } k \text{ are } 1 \text{ or } 2, \text{ and } j \neq k$$

- **Explicit Penultimate Model**

$$r_{12} \neq r_{21} \quad \text{and / or} \quad r_{22} \neq r_{11}$$

### **Implicit Penultimate Model**

$$k_{111} \neq k_{211} \quad \text{and / or} \quad k_{222} \neq k_{122}$$

$$s_1 = \frac{k_{211}}{k_{111}} \quad s_2 = \frac{k_{122}}{k_{222}}$$