①

Mechanisms: what, why and how?

What...

* A description of how A → B (or A + B → C + D etc.)
* A complete mechanism describes the structure and energy of every transition state and intermediate

Based on a hypothesis : A 'hypothetical construct'
↳ deduce consequences ['phenomenological']

Test the phenomenological consequences by experiment.
- the best experiments aim to disprove the hypothetical construct (the model)

Outcomes of experiments support or disprove the model.

More than one model leads to debate - can go on for years (decades). Often quite heated.

Proof : cannot be proven, just disproved.
when more than one model is proposed and some remain supported (not disproved) - then simplest is chosen ['Occam's Razor']
↳ currently favoured model becomes the 'accepted mechanism'

Level of detail - depends on interest in the reaction

Care must be taken in obtaining data - time consuming means money. Painstaking manner.

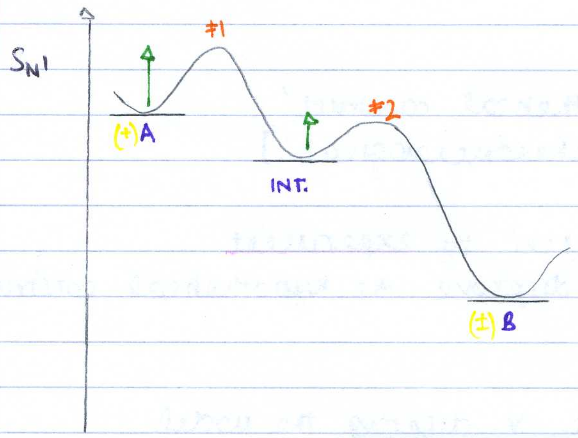
Imagination - good investigations are not bound by dogma
- think 'outside the box'

Why...

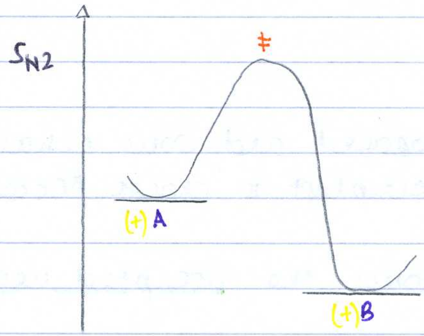
Design new catalysed or not reactions based on analogy to known
Curiosity - intellectual challenge
Optimise known reactions
Safety - don't mix A + B → 
Intellectual property - patents on processes in industry
Correlation and thus simplification

How...

Make sure identity of starting materials and products is correct (known).

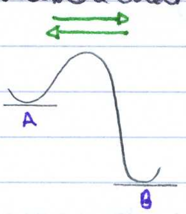


Intermediates - observe
→ must have a significant (enough) concentration.
If in low conc.
- trap: A → INT. → B
  ↓ trap (X)
  [INT—X]
- independent synthesis of intermediate. Z → INT. → B
- probe for symmetry, stereochemistry, etc.

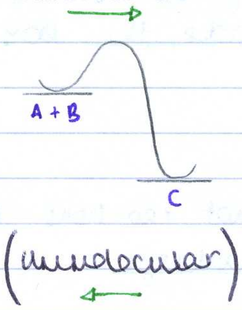


Mechanisms are constructed by linking elementary steps. Elementary steps connect starting material and product by a single transition state.

Unimolecular:



Bimolecular:



Termolecular: (and higher) entropically disfavoured ΔS

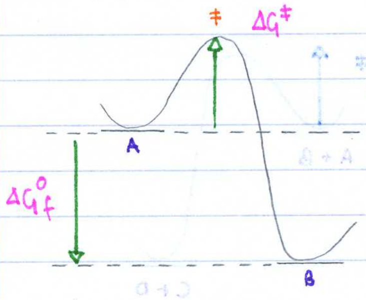
②

A + B ——[?]——▷ C

Tools :

* kinetics and thermodynamics
  k_{obs} $\Delta S^{\ddagger}$
  spectroscopy and spectrometry
* isotopic labelling - stable ^{2}H, ^{18}O, ^{13}C
  - radioactive ^{14}C, ^{3}H
* computation
* trapping intermediates
* preparing intermediates
* stereochemistry

Models for mechanism built from elementary steps (connects A and B via a single ‡)



$\Delta G^{\ddagger} = -RT \ln k \left(\frac{h}{k_B T}\right)$

A —k—▷ B

rate = k [A]

Boltzman, Planck's

$\Delta G^{\ddagger} = \Delta H - T\Delta S$ measure rate vs. T ⟹ $\Delta S^{\ddagger}$

The change in order (entropy) on reaching ‡.

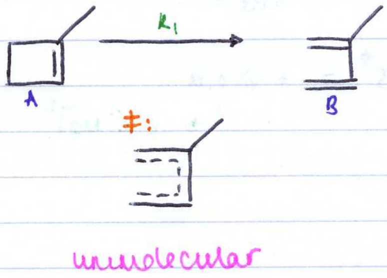
Reactions proceeding via one elementary step are called 'concerted'
→ no intermediates.

Reactions proceeding via two or more elementary steps are called 'stepwise'
→ has intermediates

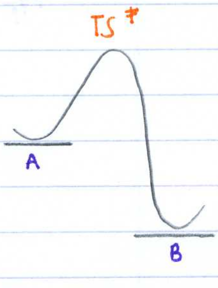
Microscopic (model)

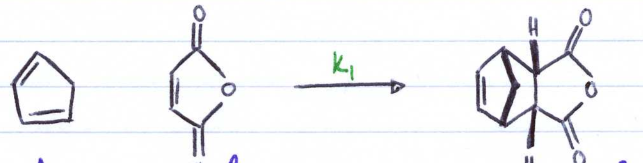
Concerted:

①



$Rate = \frac{d[B]}{dt} = k_1[A]$

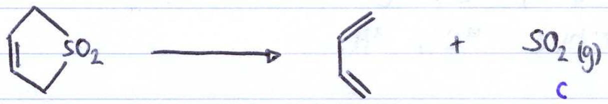


② 

A B C

bimolecular

$$\text{rate} = \frac{d[C]}{dt} = k_1[A][B]$$

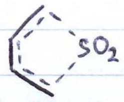
③ 

A B C

unimolecular

$$\text{rate} = \frac{d[B]}{dt} = \frac{d[C]}{dt} = k_1[A]$$

‡:



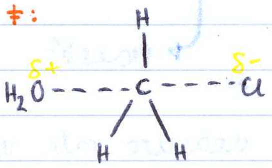
④ $CH_3Cl \xrightarrow[\Delta]{H_2O\ B,\ k_1} CH_3OH + HCl$

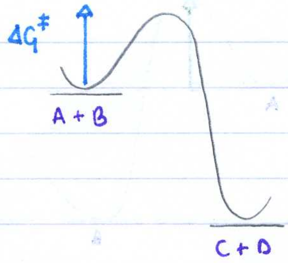
A C D

bimolecular

$$\text{Rate} = k_1[A][B]$$

‡:





Macroscopic (observed)

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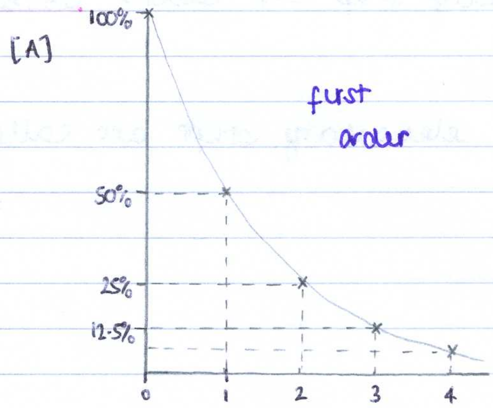
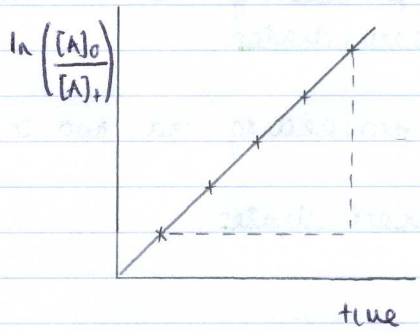




$$t_{1/2} = 1 = \frac{\ln 2}{k_{obs}} \rightarrow s^{-1}$$

k_{obs} = gradient (s^{-1})

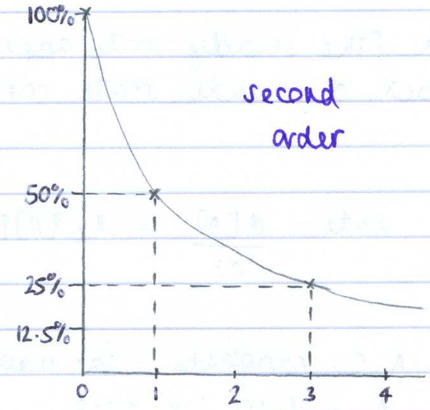
$\text{rate} = k_{obs}[A]$ $(k_1 = k_{obs})$

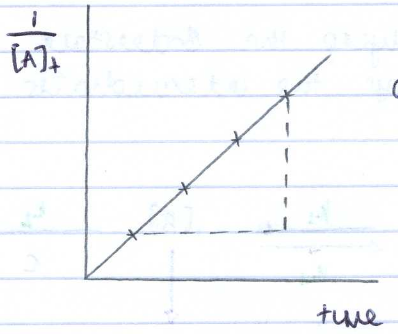
$\Delta S^{\ddagger} = +\ 8.e.u$

↳ $J\,K^{-1}\,mol^{-1}$

(small positive number)

② <u>Only for $[A]_0 = [B]_0$</u>





gradient = k_{obs} ($M^{-1}\,s^{-1}$)

no $t_{1/2}$

Rate = $k_{obs}[A][B]$

$\Delta S^\ddagger$ = −150 e.u.
(large negative number)

③ Rate = $k_{obs}[A]$; first order ; $t_{1/2}$

$\Delta S^\ddagger$ = + 60 e.u. (large positive number)

④ [second order (?)]

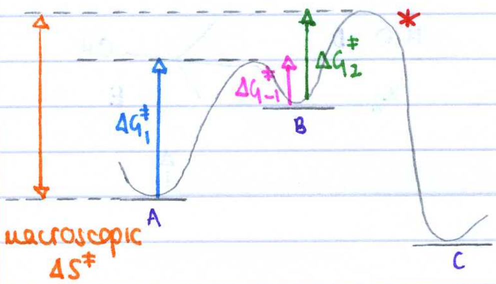
Rate = $k_{obs}[A]$
↳ psuedo first order

$\Delta S^\ddagger$ = −54 e.u.

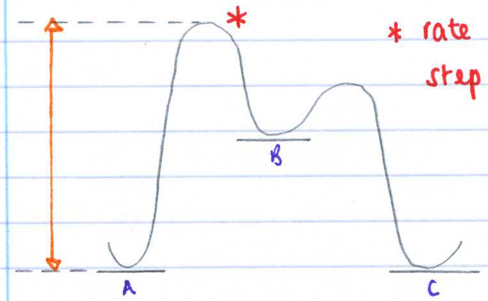
$[B] = [H_2O] = 54\ M$ = constant

$\therefore 54k_1 = k_{obs}$ ⟵ $k_1[B] = k_{obs}$

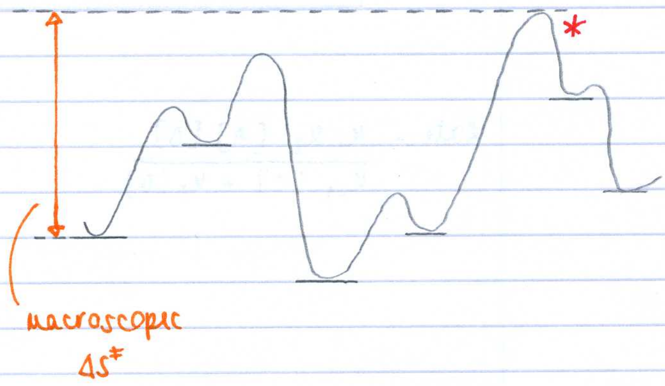
Stepwise mechanisms involve a <u>series</u> of elementary steps.



$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_2} C$$



* rate limiting step (RLS)



All species involved up to and including the RLS appear in the macroscopic rate equation (k_{obs})

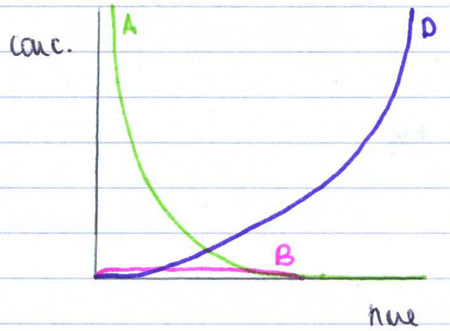
Applying the Bodenstein approximation [The steady state approximation] - says the intermediates rapidly reach a steady state concentration.

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [B] \xrightarrow[C]{k_2} D$$

[B]: low but steady conc.

$$\text{Rate} = \frac{d[D]}{dt} = k_2[B][C]$$

A, C : reagents - can measure concs.
B : very low conc.



$$k_1[A] = k_{-1}[B] + k_2[B][C]$$
$$= [B](k_{-1} + k_{-2}[C])$$

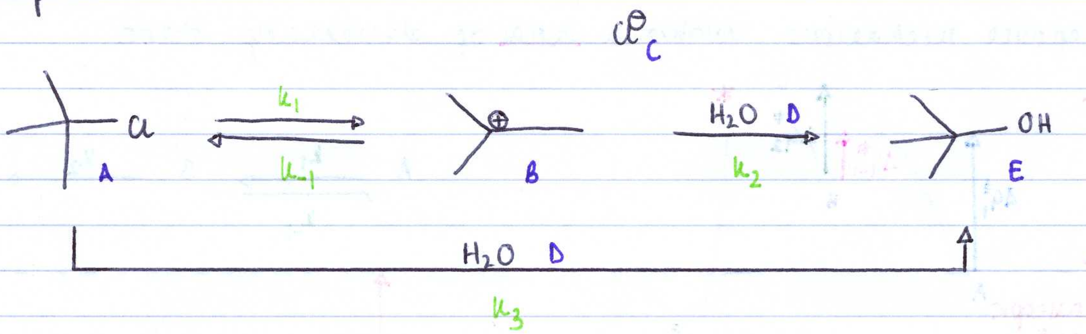
$$\frac{k_1[A]}{k_{-1} + k_2[C]} = [B]$$

put into rate equation

$$\frac{d[B]}{dt} = 0 \Rightarrow \sum(\text{making } B) = \sum(\text{destroying } B)$$

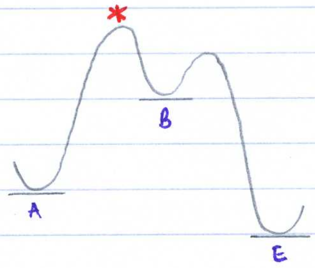
$$\text{rate} = \frac{k_1[A]\,k_2[C]}{k_{-1} + k_2[C]}$$

Example:



$$\text{Rate} = \frac{k_1 k_2 [A][D]}{k_{-1}[C] + k_2[D]}$$

(1)

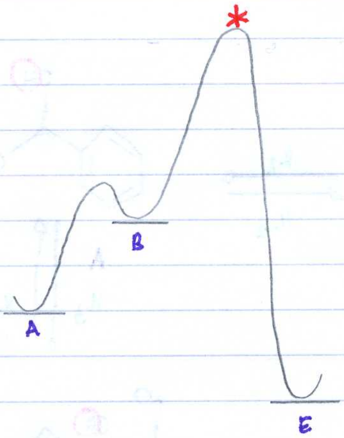


$k_2 \gg k_{-1} \Rightarrow \frac{k_1 k_2 [A][D]}{k_2 [D]}$

$= k_1 [A]$ (k_1 → $= k_{obs}$)

classic S_N1

(2)



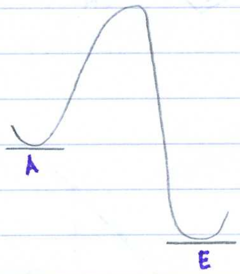
$k_2 \ll k_{-1} \Rightarrow \frac{k_1 k_2 [A][D]}{k_{-1} [C]}$

$= k_{obs} \frac{[A][D]}{[C]}$

S_N1 / S_N2 divide

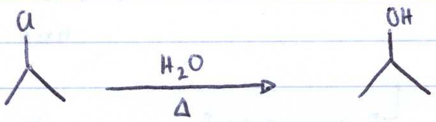
test for this by adding chloride ion ($Cl^{\ominus}$)

(3)



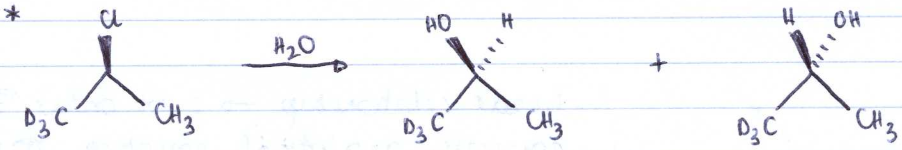
Rate $= k_3 [A][D]$ (k_3 → k_{obs})

S_N1 or S_N2?



* vary $[Cl^{\ominus}]$: no effect on rate. Eliminate (2)

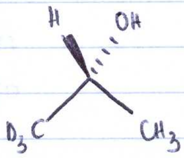
*



S_N1 50:50 mix so eliminate (1)

now chiral - need to make single enantiomer

only

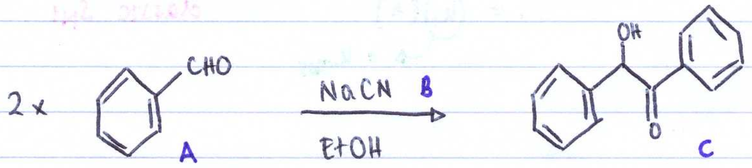


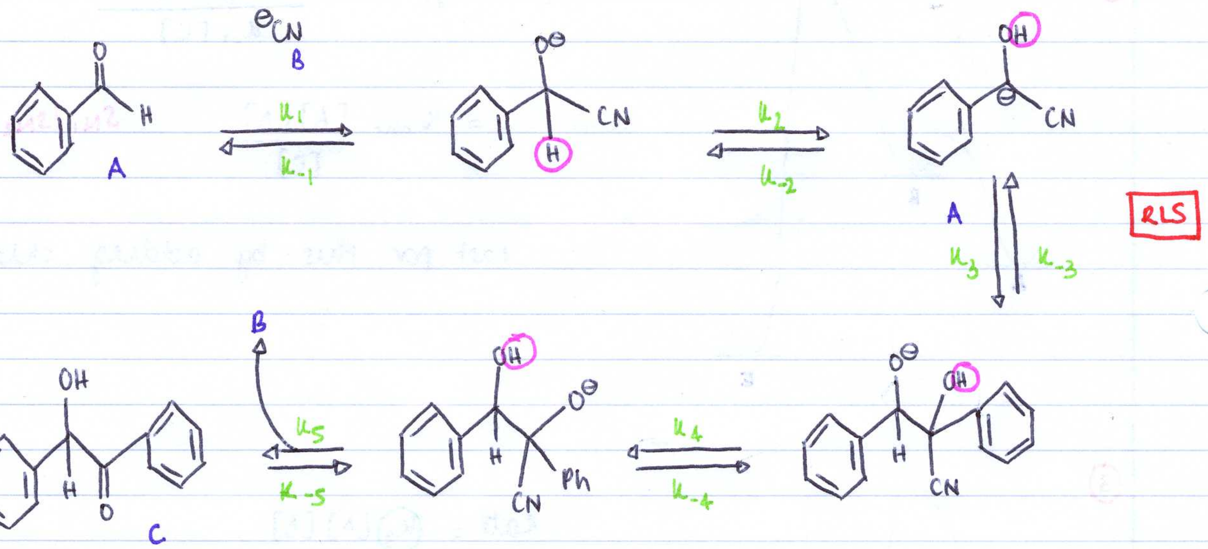
SN2 goes with inversion

* measure entropy $\Delta S^{\ddagger} = -35$ e.u. eliminate (1) support (2) (3)

More complex kinetic scenario

Benzoin reaction : ('Accepted mechanism')





Apply Bodenstein approximation...

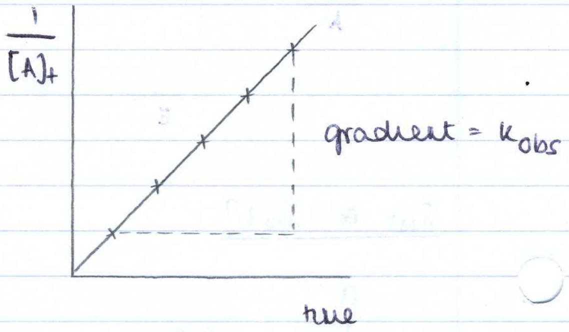
- low conc. of all intermediates

$\Rightarrow$ Rate $= \frac{-d[A]}{dt} = \frac{d[C]}{dt}$

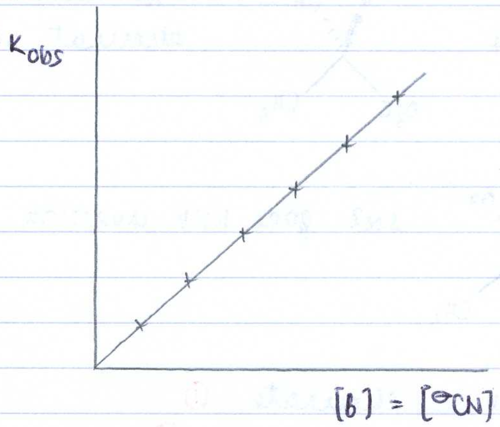
Analytical $= k_1 k_2 k_3 [A]^2 [B]^1$
(third order)

$^{\ominus}CN$ is a catalyst...

$\frac{d[^{\ominus}CN]}{dt} = \frac{d[B]}{dt}$



↳ emperical rate equation $= k_{obs}[A]^2$
psuedo second order



linear relationship → first order $^{\ominus}CN$
confirms analytical equation $[^{\ominus}CN] = [B]$

reaction only proceeds in the presence of a catalyst - 0 intercept.

(5)

Electronic effects: Hammett correlations (linear free energy relationships)

Concept: A ⟶ B How to study electronic influence on rate?

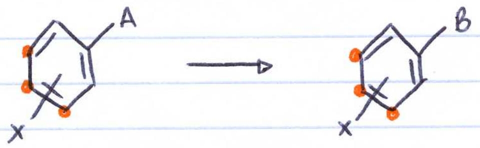
i) Attach a linker:

ii) Ensure linker does not change steric environment. (or constant steric environment)

iii) Systematically and remotely change electronics

X_1, X_2, X_3, etc.

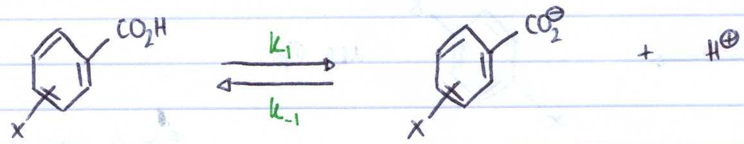
iv) Measure effect on rate



meta, para - not ortho (too close to reaction centre)

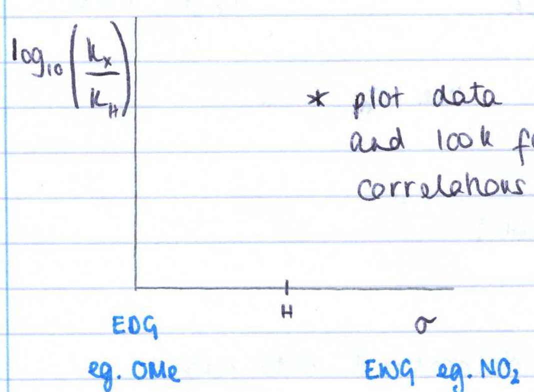
Based system on benzoic acids...

$$K_1 = K_a = \frac{[ArCO_2^{\ominus}][H^{\oplus}]}{[ArCO_2H]}$$



(at equilibrium)

Apply this to rates...



* plot data and look for correlations

σ values from tables:

eg. X = NO_2 σ = 0.78

X = H σ = 0

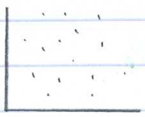
* Rule of thumb:

$$\frac{\text{rate } NO_2}{\text{rate } MeO} \approx 10^{\rho}$$

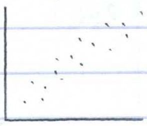
⟶ rho - gradient of correlation

* Is there a straight line correlation?

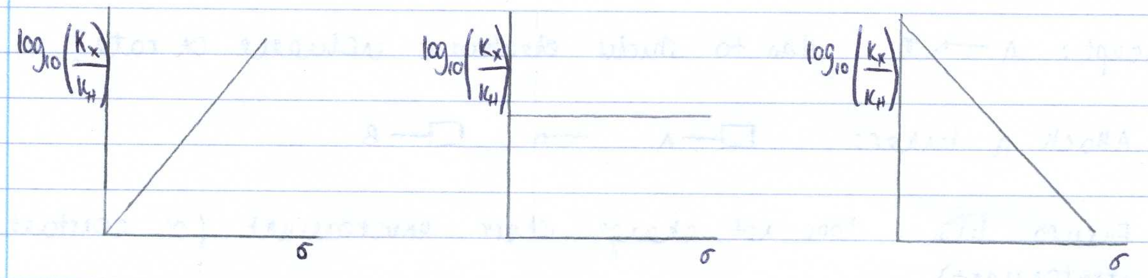
No: mechanism different for all or most X.



Yes: mechanism is same for all X (good news!)



* is gradient positive, zero or negative ?

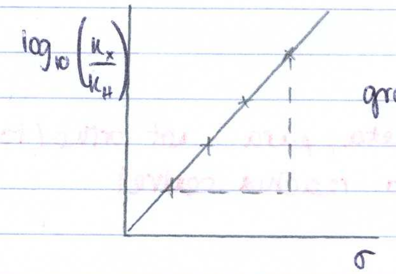


EWG: negative charge increase at ‡

No effect: no charge build up at ‡

EDG: positive charge increase at ‡

* magnitude tells you how sensitive



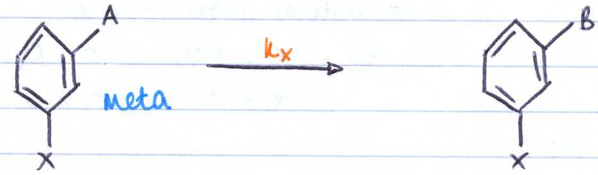
gradient = ρ (rho)

Hammett corellations

use σ_p

or/and

or/and

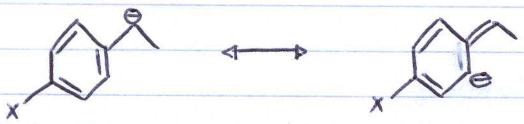


use σ_m

For a series of X_1 X_2 X_3
Measure rate ⇒ k_x
Compare with:
(k_H) X = H

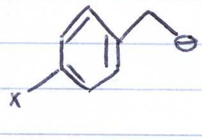
Each X has its own σ-values (table)
* special cases ! $\sigma_p^{\oplus}$, $\sigma_p^{\ominus}$

$\sigma_p^{\ominus}$: when negative charge can be delocalised onto ring



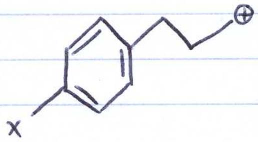
$\sigma_p^{\ominus}$

But :



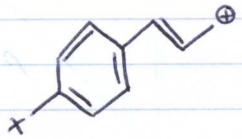
not on ring σ_p

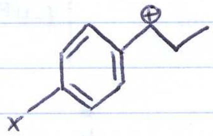
same for $\sigma_p^{\oplus}$:



σ_p

If no $\sigma_p^{\oplus}$ available for a X, use σ_p.



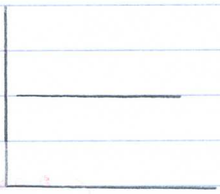


$\sigma_p^{\oplus}$

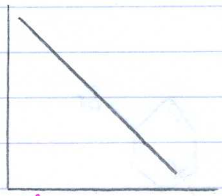
Look for correlations: $\log_{10}\left(\frac{k_X}{k_H}\right) = \rho\sigma$; $\frac{\text{rate } X = NO_2}{\text{rate } X = OMe} \simeq 10^{\rho}$

eg. $\rho = 6 \Rightarrow NO_2 \Rightarrow 1 \times 10^6$ faster than OMe

$\rho = -6 \Rightarrow NO_2 \Rightarrow 1 \times 10^6$ slower than OMe

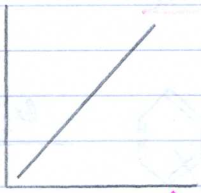


$\rho = 0$



ρ = -ve

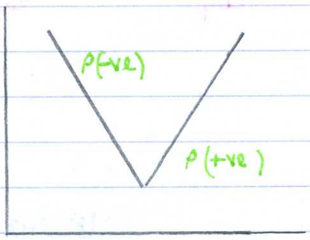
EDG faster



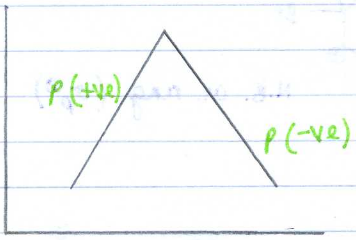
ρ = +ve

EWG faster

Also:

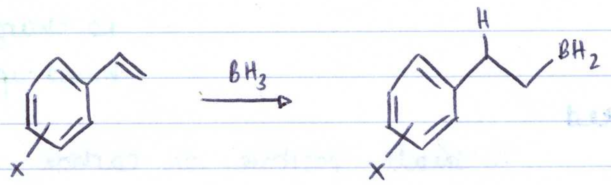


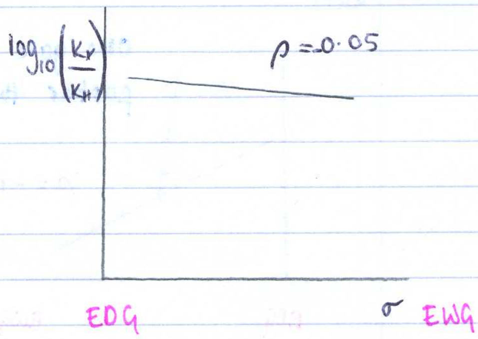
valley: change in mechanism



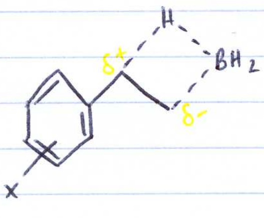
hill: change in rate limiting step

$\rho \approx 0$

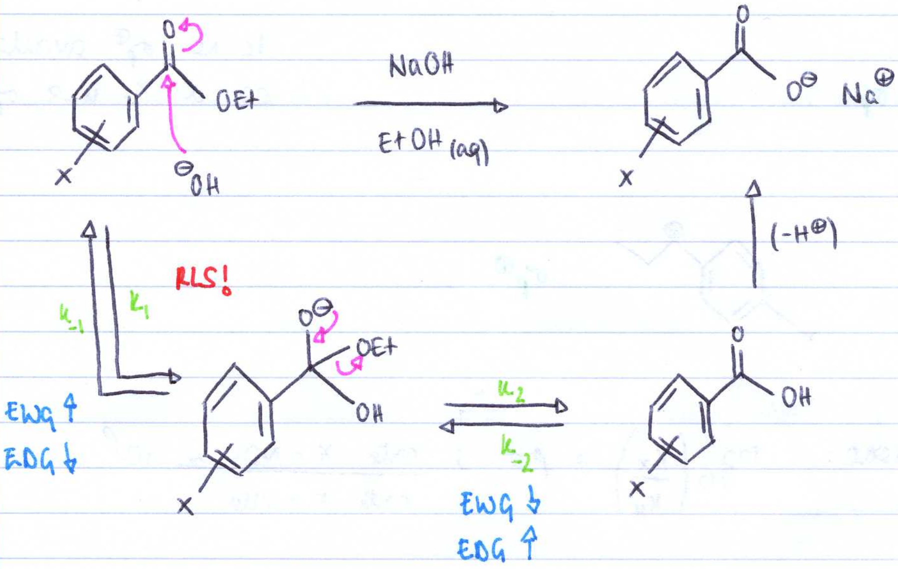


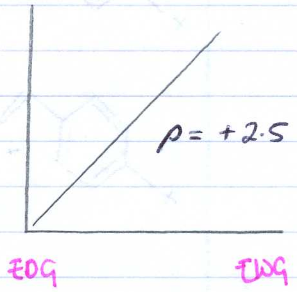


small charge build up...

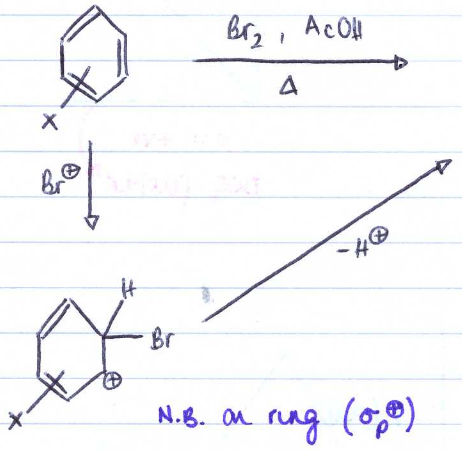


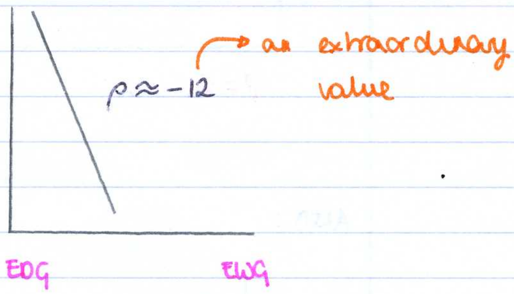
$\rho \approx +ve$

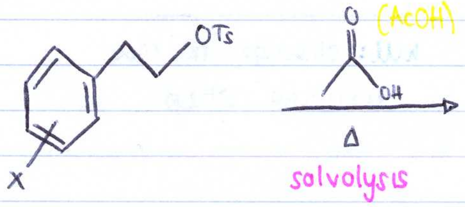




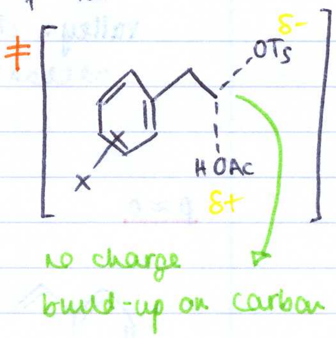
$\rho = -ve$



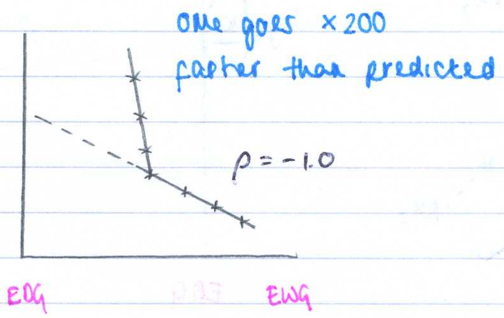




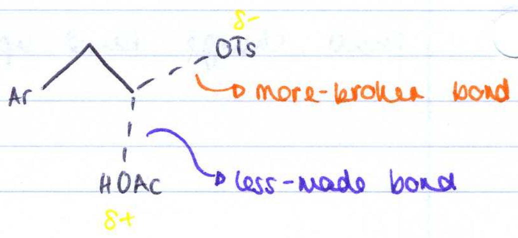
If SN2:



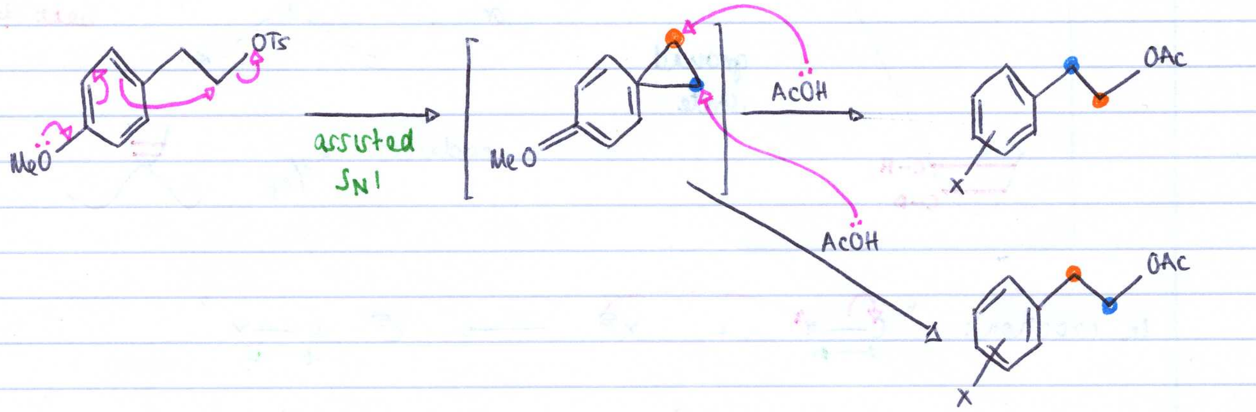
BUT:



∴ small positive on carbon



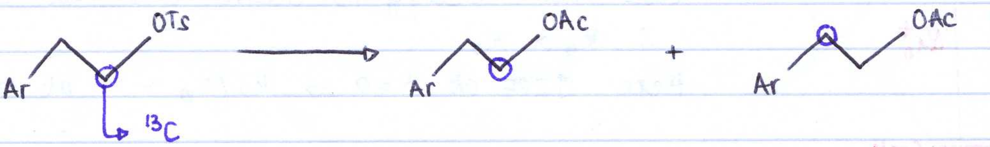
valley : change in mechanism



use of isotopes for mechanistic study

'labelling' : to mark positions and track through reactions

eg.



[see last lecture]

'kinetic isotope effects' : isotope affects rate of reaction
largest for ^1H, ^2H, ^3H
much smaller for heavier atoms ^{12}C, ^{13}C, etc.

Four basic types...

* primary (1° KIE) C–H / C–D bond broken in reaction
k_H / k_D = KIE – up to ca. 7 at room temperature

* secondary (2° KIE) H, D close to reacting centre [α, β]

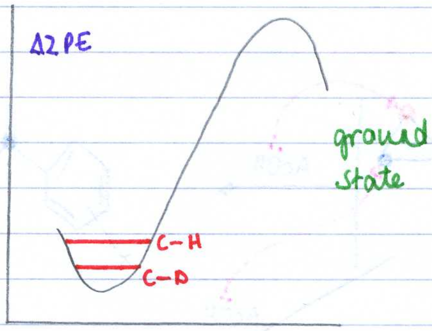
* steric (C–D smaller than C–H)

* solvent (XH ; XD) X—H/D broken

Primary isotope effect C–H vs. C–D

C–H longer than C–D.

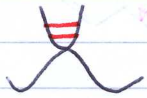
C–H	C–D	
⟷	⟷	$\frac{3000}{2100} \approx \sqrt{2}$
$\approx 3000\ cm^{-1}$	$\approx 2100\ cm^{-1}$	



If "C - - - H - - - - - - - X" late ‡

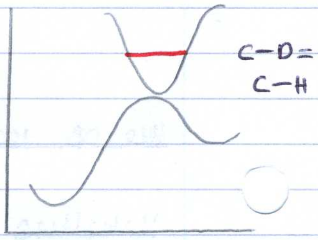
or " C - - - H - - - X " bent ‡

reduces k_H/k_D

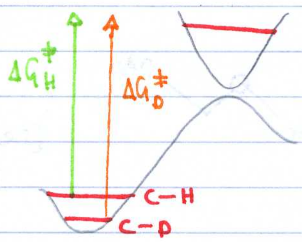


In reaction: " C—H + $X^{\ominus}$ ⟶ $C^{\ominus}$ H—X "

At ‡ $[C - - - H - - - X]^{\ominus}$ No H movement
rotational perfect symmetry

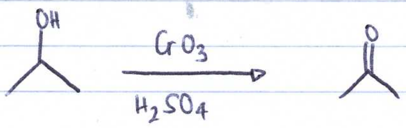


∴



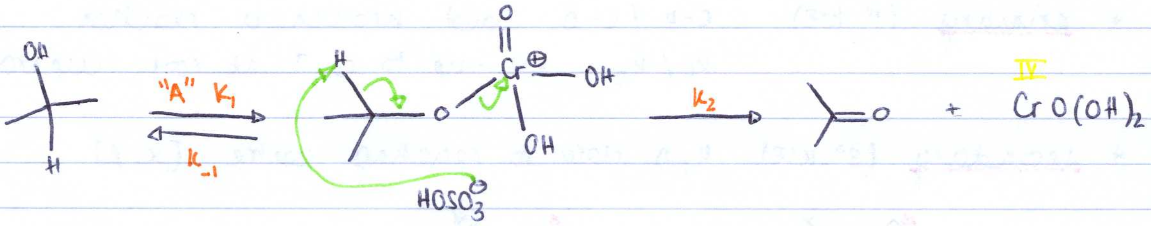
costs more energy to cleave C–D than C–H
∴ $k_H > k_D$
Here ΔZPE at ‡ = 0 ⇒ $k_H/k_D \sim 7$ at room temp.

Example use: Jones oxidation



accepted mechanism:

$\overset{VI}{CrO_3} + H_2SO_4 \rightleftharpoons [HSO_4^{\ominus}\ HO\overset{\oplus}{Cr}O_2]$ "A"



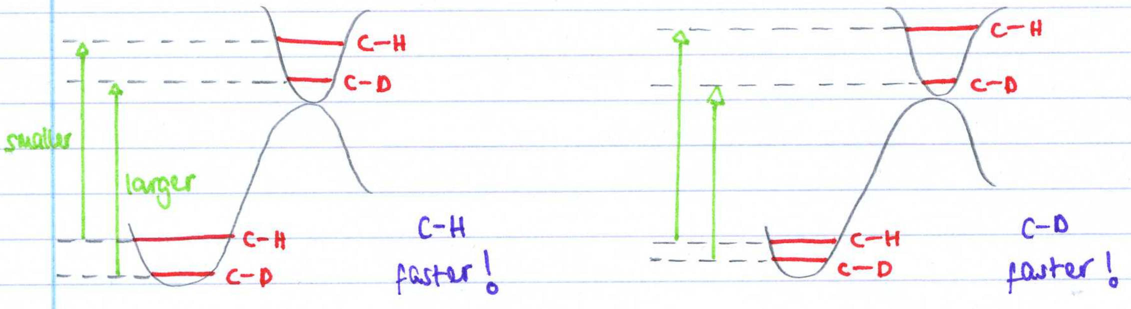
If k_1 = RLS no C–H cleavage ∴ $k_H/k_D = 1$
If k_2 = RLS C–H cleavage ∴ $k_H/k_D \approx 7$

In this example:

reacts ~7 times slower
⟶ k_2 is RLS

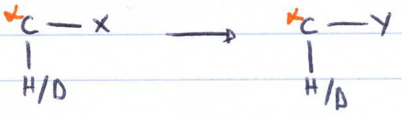
⑧

Secondary isotope effect arises from 'difference of differences'



Two major cases of ΔΔZPE :

* change in hybridisation at (α)

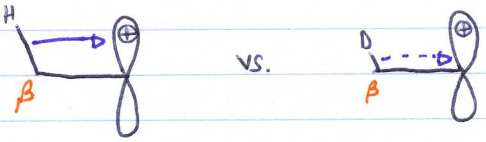


out of bend plane

$sp^2 \approx 800\,cm^{-1}$ $sp^3 \sim 1350\,cm^{-1}$

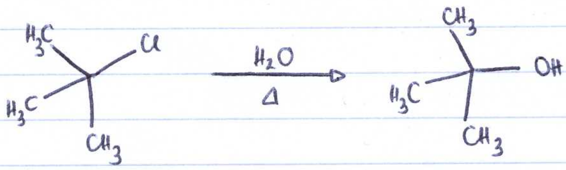
eg. $sp^3 \rightarrow sp^2$	p character ↓	$k_H > k_D$	~15% max	$k_H/k_D \sim 1.15$
$sp^2 \rightarrow sp^3$	p character ↑	$k_D > k_H$	~15% max	$k_H/k_D \sim 0.85$.

* Hyperconjugation at (β)



shorter C–D → poorer overlap
$k_H/k_D \sim 1.4$ max

eg.



$k_H/k_D \simeq 2.6$ each C–H 10% rate

vs.