GCLJ 1
lecture 1/6

24/1/2011

The Determination of Reaction Mechanisms

This course is not about learning mechanisms (or facts and figures).
Handout not examined – data given in exams.
The exam will feature a mechanism you haven't seen – so focus on understanding.

Mechanisms can't be proved, only accepted. Some mechanisms you've learned at Bristol are probably wrong – but we don't know they're wrong yet.

What, why, how, what:

- What: mechanism is a hypothetical construct (ie. a model) – of every: [species, rate, energy, structure, solvation*]

  (This ideal level of detail is known for almost no reaction.)

  ⇒ predict phenomenological consequences (outputs)
  ↳ what does the model predict will happen as you change the conditions (conc, temp, etc.)

  ⇒ test via experiment
  – good experiments challenge the model

  failure of test (wrong prediction made) leads to rejection of the model

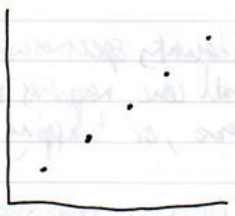
  ⇒ often more than one model fits the experimental data...

  ⇒ debate of model in literature... can be quite heated

if there is one model (only) that fits: the "accepted mechanism"

if there is more than one that fits: the simplest is usually "accepted"

Occam's razor = simplest is best.



data

unnecessarily complicated model!

simpler model – accepted until new data suggests otherwise.

Proof: mechanisms cannot be proven, only disproven.

* Detail: data – limited by experimental tools available at the time.
– limited by time / interest (= money)

Care: painstaking collection of data sets required. – accurate and large datasets, takes time and costs money

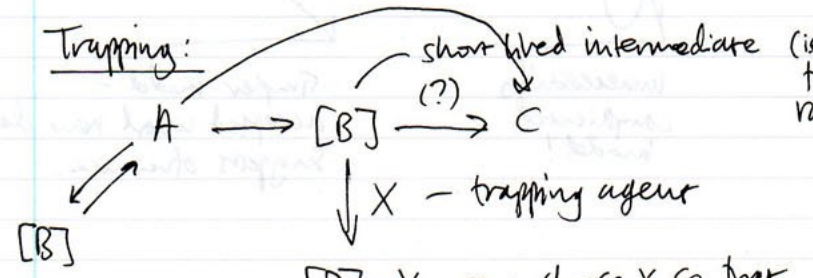
Imagination: good mechanistic investigators are able to "think outside the box" – ie. escape from dogma.

Why... bother working out mechanisms?

- Reaction optimisation (in terms of rate, yield, selectivity, fewer side products, "better", "cleaner" chemistry)
- Predict – outcome of similar reactions
– new chemistry, reactions never before conceived.
– what won't work
– scalability
– safety – can thermodynamics help predict possibility of explosions or other unsafe events
– side products (especially if eg. carcinogenic – helps safety)
- Intellectual property issues
- Curiosity
- Correlate reactions – group them together by shared / similar mechanisms into classes
– allows us to simplify our understanding of chemistry.

How
- Identity of product(s) and also the identity of any intermediates (!!) – many cases in early literature before NMR, IR, etc, where wrong product identified.
  - long-lived – enough to identify spectroscopically or isolate
  - short-lived – vanishingly small conc. requires v. fast spectroscopic tools to observe, or trapping

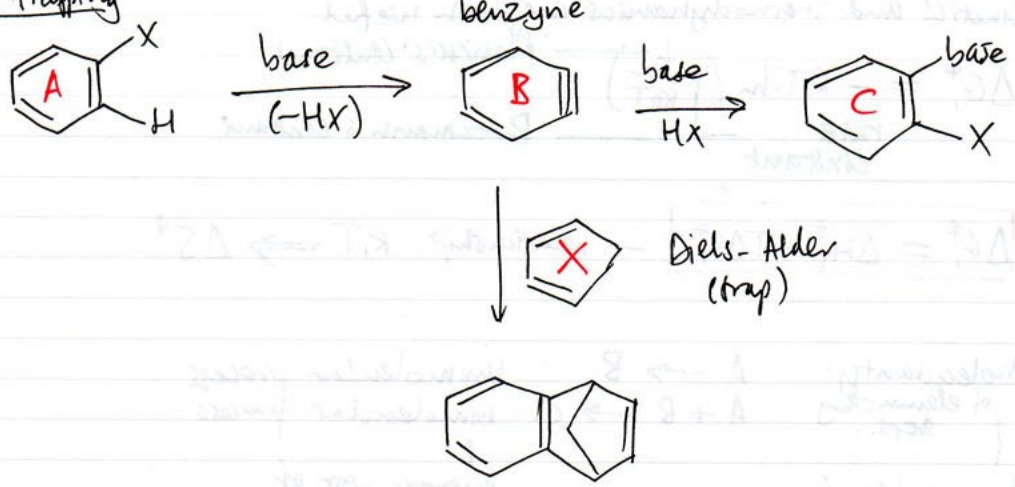
Trapping:



(ie. very reactive ∴ can get it to react with a trapping agent X rather than forming C)

biggest danger is that [B] is present but not involved in A → C – can lead to false conclusions.

Example of trapping



Tools for determining reaction mechanisms.

- Spectroscopy / spectrometry (MS, IR, NMR, UV, etc.)
- Isotopic labelling – stable (^{2}H, ^{13}C, ^{10}B, etc.) ← more common today
  – hot (^{3}H, ^{14}C ... (radioisotopes) easy to detect but dangerous
- Kinetics / thermodynamics.
- Computation – becoming very important

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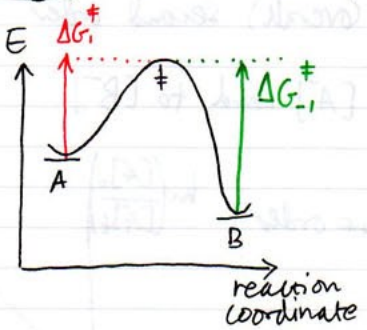
Reaction Kinetics / models

- Models are constructed from one or more elementary steps.
- Elementary steps connect starting material A with product B via a single transition state ‡.



e.g. $A \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} B \xrightarrow{K_2} C$ n.b. k is not K

transition state characterised by lifetime less than 10^{-13} s, any change in geometry leads to decrease in energy.

principle of microscopic reversibility says

$A \rightarrow B$
$B \rightarrow A$] via same path (‡)

K_1, K_2 etc are microscopic rate constants.

⇒ use in an analytical rate equation.

For this example, rate $= \frac{K_1 K_2 [A]}{K_{-1} + K_2}$ (see later for derivation).

Kinetics and thermodynamics are both useful

$$\Delta G_1^{\ddagger} = -RT \ln\left(K \frac{h}{k_B T}\right)$$

K: rate constant; h: Planck's constant; k_B: Boltzmann's constant

$$\Delta G_1^{\ddagger} = \Delta H_1^{\ddagger} - T\Delta S_1^{\ddagger}$$ — relationship $K_1 T \Longrightarrow \Delta S^{\ddagger}$

Molecularity: of elementary steps.

the number of species involved in an elementary step.

$A \rightarrow B$: unimolecular process

$A + B \rightarrow C$: bimolecular process

entropic cost of bringing 3 species together for an elementary step is so high that it is very rarely encountered

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

Step 1: unimol.
Step 2: bimol. (k_2)

Macroscopic — what we measure

- rate = k_{obs} ... macroscopic rate constant

$$\text{rate} = k_{obs}[A]^x[B]^y[C]^z$$ empirical rate equation

reaction order : x, y, z

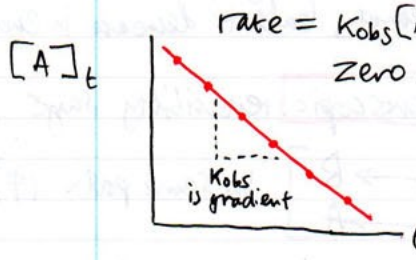
e.g $\text{rate} = k_{obs}[A]$ (overall) first order reaction

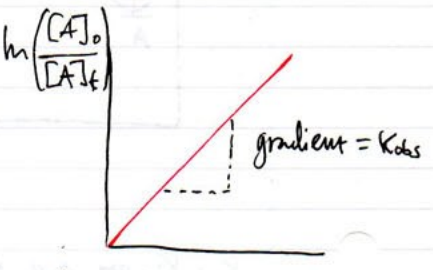
$\text{rate} = k_{obs}[A][B]$ (overall) second order

first order with respect to [A] and to [B].

$\text{rate} = k_{obs}[A]^0$

zero order (or pseudo-zero order)



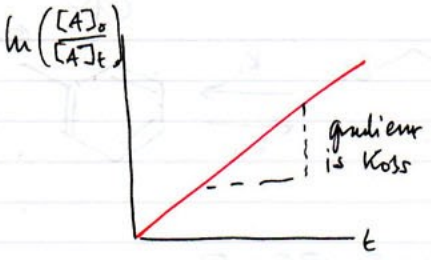


first order or pseudo first order reaction

Zero order

(or pseudo-zero order)

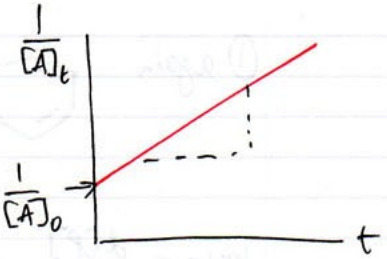
rate = $k_{obs}[A]^0$



first order

(or pseudo first order)

rate = $k_{obs}[A]^1$



second order.

(or pseudo-second order).

rate = $k_{obs}[A]^2$

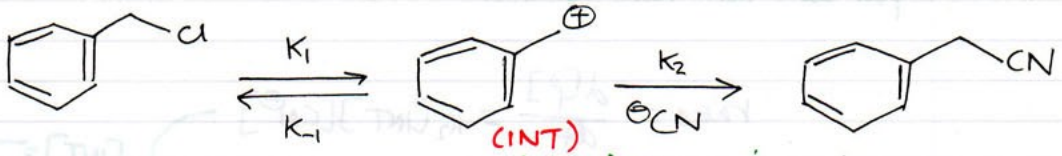
{if $[A]_0 = [B]_0$}

Key relationship between macroscopic and microscopic: ~~species~~

all species involved up to and including the rate-limiting step (RLS) appear in the empirical rate equation (sometimes in k_{obs})

Example analysis

- possible (reasonable) mechanisms

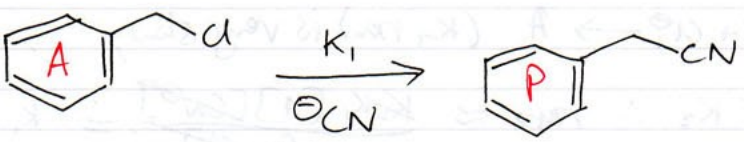
① 

two steps, S_N1 mechanism.

rate = $\frac{d[P]}{dt} = k_2[INT][CN]$

(INT) may be present in v. low conc. ∴ v. difficult to detect, let alone measure [INT] ∴ apply SSA — Bodenstein approximation [INT] is low, steady.

(k_{-2} rxn possible but very slow ∴ neglect for simplicity.

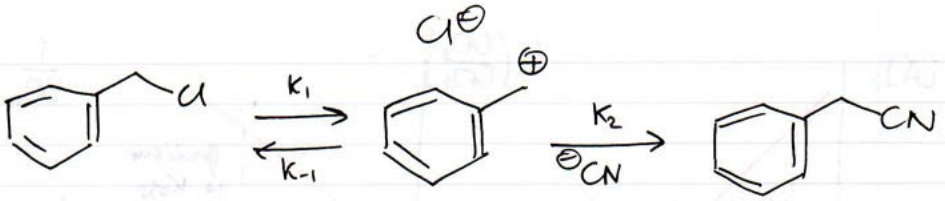
② 

one step, S_N2 mechanism.

rate = $\frac{d[P]}{dt} = k_1[A][CN]$ ∴ $k_{obs}[A][CN]$ $k_1 = k_{obs}$

microscopic macroscopic

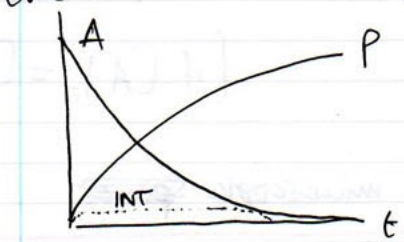
① again.



$$\text{rate} = \frac{d[P]}{dt} = k_2[INT][CN^-]$$

Steady State: [INT] low conc.

Bodenstein approximation: rate of production of INT = rate of consumption.



$$k_1[A] = k_{-1}[INT][Cl^-] + k_2[INT][CN^-] \quad \leftarrow \text{Steady State approximation}$$

$$= [INT](k_{-1}[Cl^-] + k_2[CN^-]).$$

derive expression for [INT]

$$\therefore [INT] = \frac{k_1[A]}{k_{-1}[Cl^-] + k_2[CN^-]}$$

put back into rate equation:

$$\text{rate} = \frac{d[P]}{dt} = k_2[INT][CN^-]$$

$$[INT] = \frac{k_1[A]}{k_{-1}[Cl^-] + k_2[CN^-]}$$

$$\therefore \boxed{\text{rate} = \frac{k_2 k_1[A][CN^-]}{k_{-1}[Cl^-] + k_2[CN^-]}}$$

analytical rate eqn for case ①

assume $INT + Cl^- \longrightarrow A$ (k_{-1} rxn) is very slow,

(i) then $k_{-1} \ll k_2$ $\therefore$ rate $\approx \frac{k_2 k_1[A][CN^-]}{k_2[CN^-]} = k_1[A]$.

(ii) assume $k_{-1} \gg k_2$ $\therefore$ rate $\approx \frac{k_2 k_1[A][CN^-]}{k_{-1}[Cl^-]}$ - actually very rare for Cl^-

For (1), either : $\text{rate} = \dfrac{k_1 k_2 [A][CN^\ominus]}{k_{-1}[Cl^\ominus]}$

distinguish from genuine S_N2 rxn by examining the effect of $[Cl^\ominus]$ by adding e.g. LiCl.

or: $\text{rate} = k_1[A]$ simple classic S_N1 $k_{obs}[A]$.

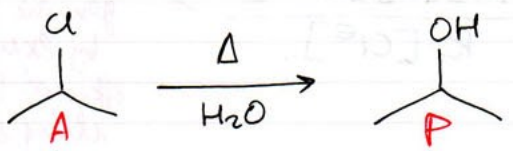
$$\text{rate} = \frac{k_1 k_2}{k_{-1}} \frac{[A][CN^\ominus]}{[Cl^\ominus]} \qquad \frac{k_1}{k_{-1}} = K \text{ equm constant for.}$$

$$= \frac{K k_2 [A][CN^\ominus]}{[Cl^\ominus]}$$

in this complex case, $[Cl^\ominus]$ builds up as rxn progresses (as Ph–Cl is consumed) and so according to mechanism (1)(ii), behaves as simple second order only for the first 20% (or so) of the reaction.

		first order	second order	common ion inhibition?
S_N2	$A \xrightarrow[RLS]{k_1} P$ ($CN^\ominus$)	×	✓	×
S_N1	$A \xrightarrow[RLS]{k_1} INT \xrightarrow[FAST]{k_2} P$ ($CN^\ominus$)	✓	×	×
S_N1/S_N2 divide (often v. hard to distinguish)	$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} INT \xrightarrow[RLS]{k_2} P$ ($CN^\ominus$, $Cl^\ominus$)	×	✓ initially	✓

Another 'simple' example.



(+ HCl)

S_N1, S_N2, or S_N1/S_N2

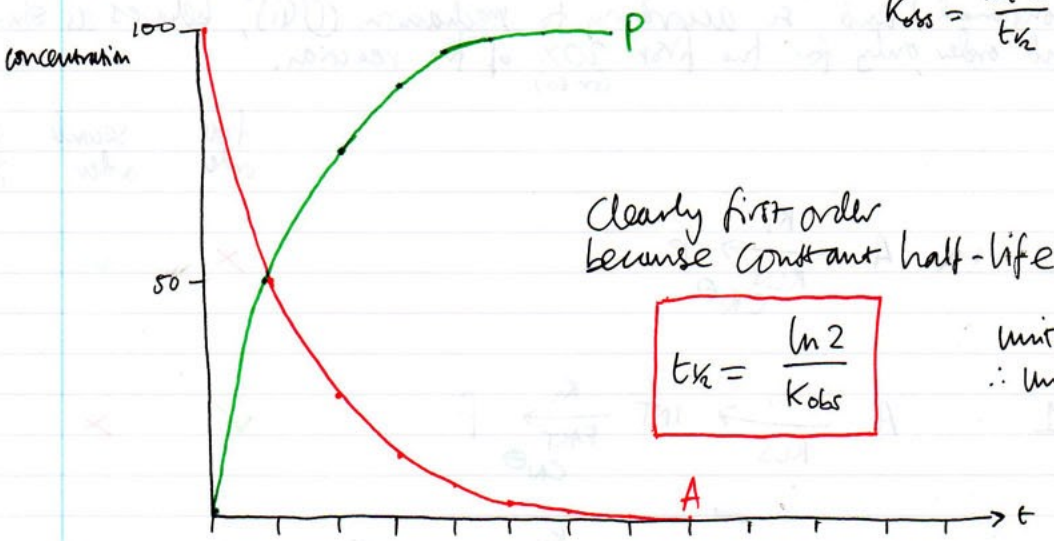
nothing to do with whether it goes via inversion, etc. Just relates to the kinetics.

S_N1 : $\text{rate} = \frac{d[P]}{dt} = k_1[A]$

S_N2 : $\text{rate} = \frac{d[P]}{dt} = k_1[A][H_2O]$

S_N1/S_N2 divide : $\text{rate} = \frac{d[P]}{dt} = \frac{k_1k_2[A][H_2O]}{k_{-1}[Cl^\ominus] + k_2[H_2O]}$

some data.



$k_{obs} = \frac{\ln 2}{t_{1/2}}$

Clearly first order because constant half-life, $t_{1/2}$

$$t_{1/2} = \frac{\ln 2}{k_{obs}}$$

units of $t_{1/2}$: s
∴ units of k_{obs} : s^{-1}

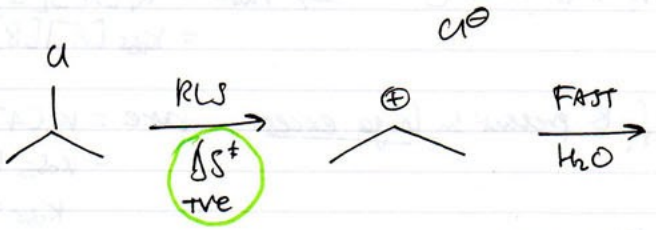
We can exclude S_N1/S_N2 because the half-lives are constant – whereas this model predicts a rxn that goes from pseudo-first order to complicated quickly as $[Cl^\ominus]\uparrow$

Can't distinguish S_N1 and S_N2 because S_N2 would likely be showing pseudo-first order behaviour ($[H_2O]$ constant if present in vast excess, e.g. solvent).

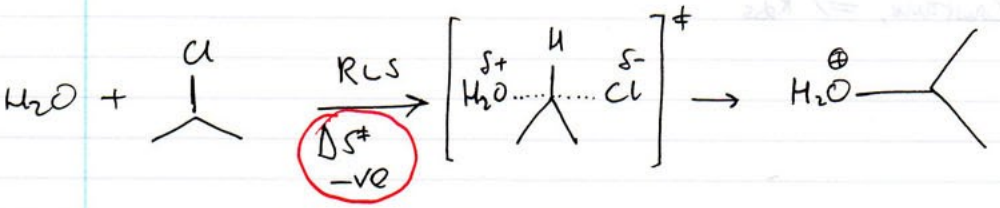
$k_1[A][H_2O] = k_{obs}[A]$, $\quad k_{obs} = k_1\underbrace{[H_2O]}_{\text{constant.}}$

$\Delta G^\ddagger = -RT\ln\left(k\frac{h}{k_BT}\right) = \Delta H^\ddagger - T\Delta S^\ddagger$ – measure rate at different temperatures to extract $\Delta H^\ddagger$ and $\Delta S^\ddagger$ – to distinguish S_N1 from S_N2

from plot of $\ln\left(\frac{k}{T}\right)$ vs. $\frac{1}{T}$, get $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$

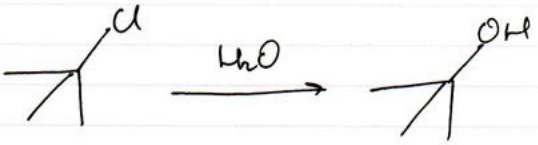


S_N1.



$\Delta S^{\ddagger} = -50\ kJ\ mol^{-1}$

$\therefore S_N2$.



$\Delta S^{\ddagger} = +60\ kJ\ mol^{-1}$

$\therefore S_N1$

$A + B \xrightarrow{k_1} C$; rate $= k_1[A][B] = k_{obs}[A][B]$

only if $[A]_0 = [B]_0$.

Solution: use large excess of A or B.

$[A]_0 = 0.01\ M$ $[A]_\infty = 0$ (100%)

$[B]_0 = 1.00\ M$ $[B]_\infty = 0.99\ M$ (1%) $\Rightarrow \frac{d[B]}{dt} \approx 0$.

$\Rightarrow$ <u>pseudo first order</u>

rate $= k_{obs}[A]$

$k_{obs} = k[B]$.

(general)

<u>Conditions where pseudo reaction orders are observed:</u>

- when the concentration of a reactant is approximately invariant throughout the reaction

Two common cases: i) one component in large excess

$A + B \xrightarrow{k_1} C \Rightarrow$ rate $= k_1[A][B]$ — second order

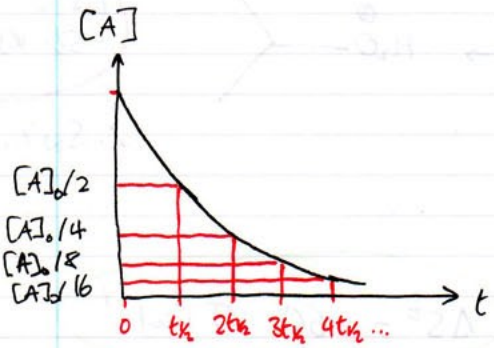
$= k_{obs}[A][B]$.

if B present in large excess: rate $= k_1[A][B]$ — pseudo first order

$= k_{obs}[A]$,

$k_{obs} = k_1[B]_0$

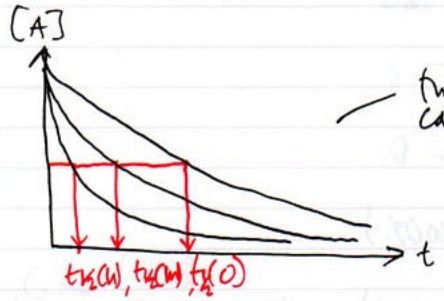
If $t_{\frac{1}{2}}$ is constant, $\Rightarrow k_{obs}$



ii) Catalyst present – and stable throughout reaction. $\therefore \frac{d[cat]}{dt} \simeq 0$

$A \xrightarrow[k_1]{CAT} B$ rate $= k_1[A][CAT]^x$

$\longrightarrow k_{obs}[A]$; $k_{obs} = k_1[CAT]^x$



three different catalyst concentrations; pseudo first order decay.

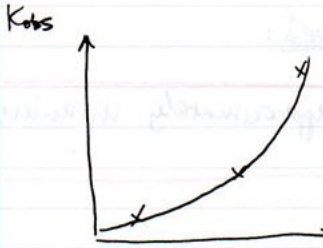
[cat] = n, m, 0

three different half lives.

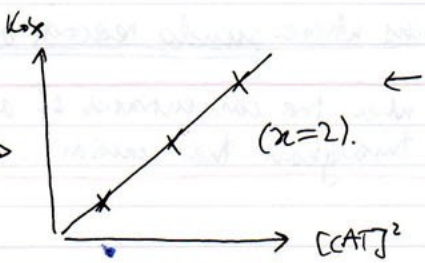
EITHER:

power 1 ∴ 1 catalyst molecule involved in RLS ($x = 1$)

OR:

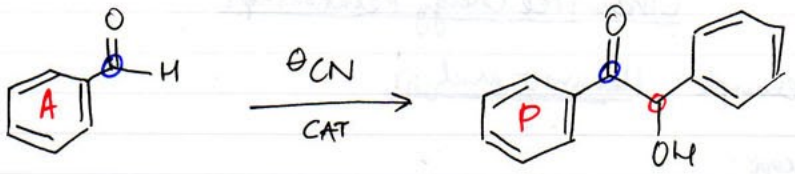


$\Longleftrightarrow$

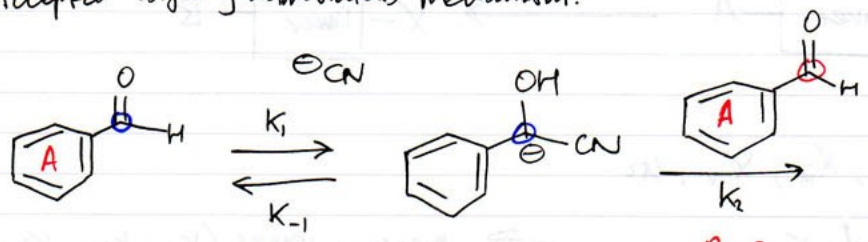


← then two catalyst molecules in RLS ($x = 2$)

Benzoin Condensation



Accepted (slightly abbreviated) mechanism:

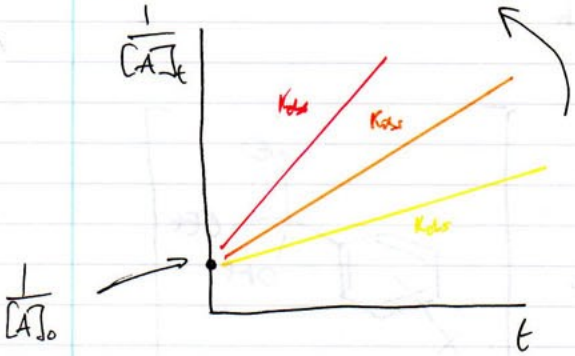


rate $\simeq K_1 K_2 [A]^2 [CN^\ominus]^1$ — $[A]^2$ because two molecules of A react with each other.

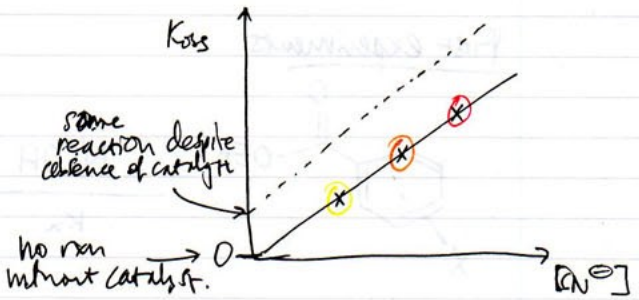
$\Rightarrow K_{obs} [A]^2$

pseudo second order, $K_{obs} = K_1 K_2 [CN^\ominus]$

Must know these three plots:
- Zero order – plot $[A]$ vs. t
- First order – plot $\ln[A]$ vs. t
- Second order – plot $1/[A]$ vs. t



increasing $[CN^\ominus]$

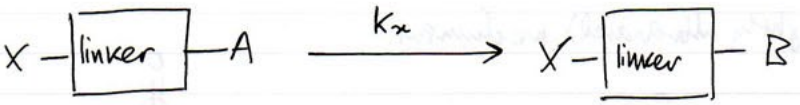


if intercept is non-zero, you have both a catalysed and an uncatalysed rxn going on.

Linear Free Energy Relationships.

- Look at one example: **Hammett analysis.**

Hammett's concept:

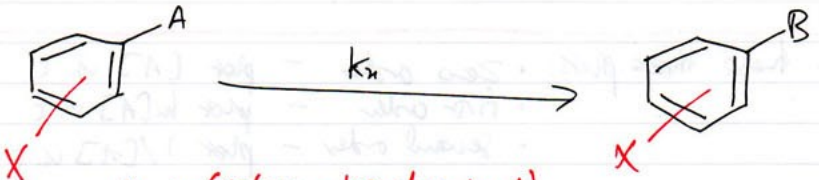


X_i, X_{ii}, X_{iii}, X_{iv}, etc.

a series of X $\Longrightarrow$ measure rates (k_{x_i}, $k_{x_{ii}}$, $k_{x_{iii}}$, $k_{x_{iv}}$,)

X must be far enough from A → B to not have a steric impact but only electronic

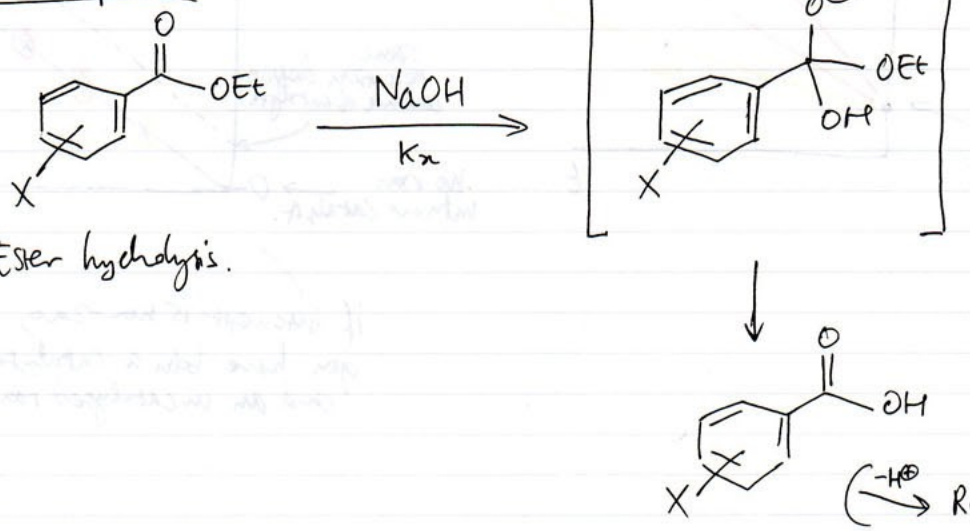
Hammett chose p- and m- substituted aromatic rings.



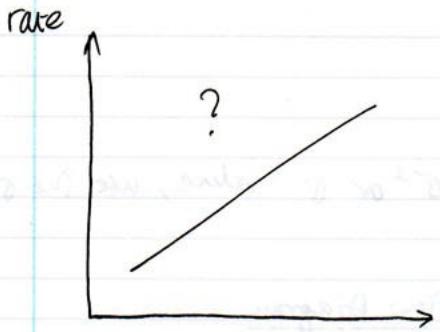
m, p (not o - too close to A)

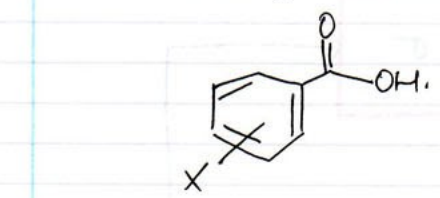
X must also be inert through the reaction

First experiments:



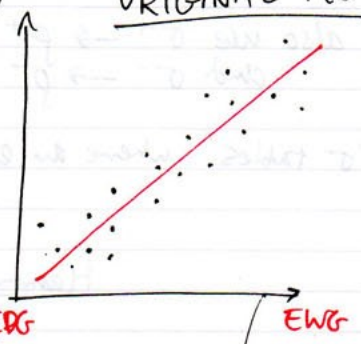
Ester hydrolysis.





$\log_{10}\left(\frac{k_x}{k_H}\right)$

ORIGINAL PLOT



- nice linear relationship between acidity and rate of hydrolysis.

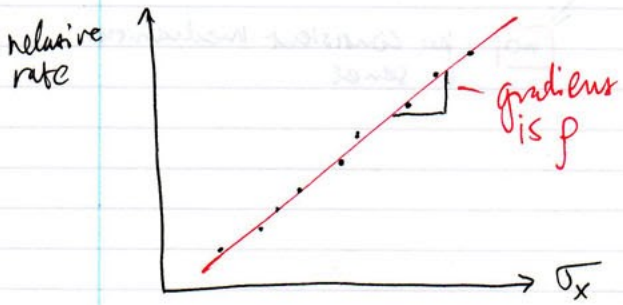
$\log_{10}\left(\frac{K_a(X)}{K_a(H)}\right)$

$-(pK_a(X) - pK_a H)$

right hand end of axis: EWGs (∵ make acidity go up)

published this ie to get σ_x (not a fudge, just altering definition to get consistently straights lines across all reactions).

MODERN PLOT



Three types of sigma value: σ_x ; $\sigma_x^{\oplus}$; $\sigma_x^{\ominus}$

$$\log_{10}\left(\frac{K_x}{K_H}\right) = \rho\sigma$$

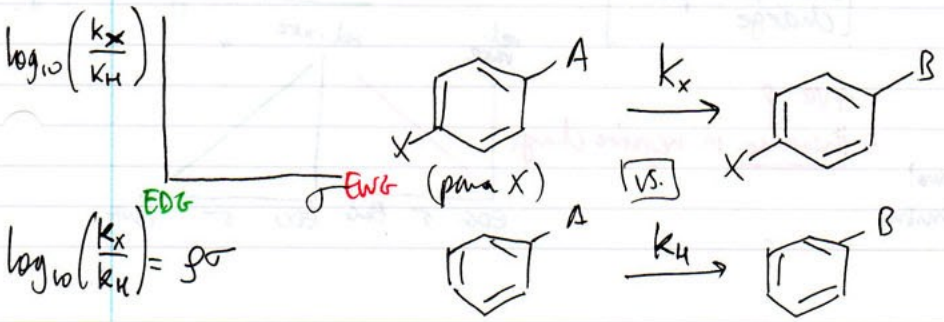
- report as $\rho^{\oplus}\sigma^{\oplus}$ or $\rho^{\ominus}\sigma^{\ominus}$ if appropriate.

Hammett "rho" value (depends on rxn)

substituent constant

3/2/2011

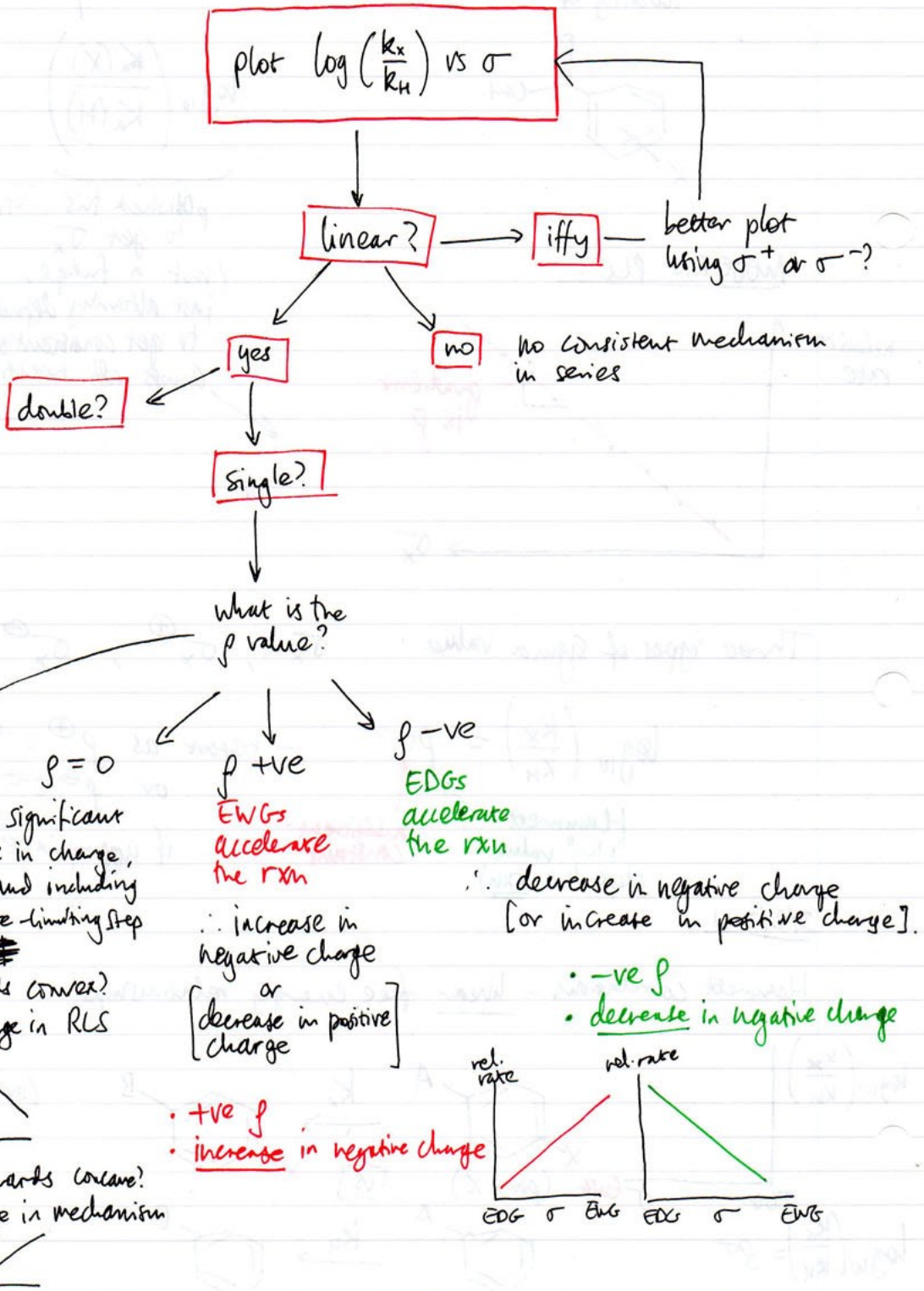
Hammett correlations – linear free energy relationships

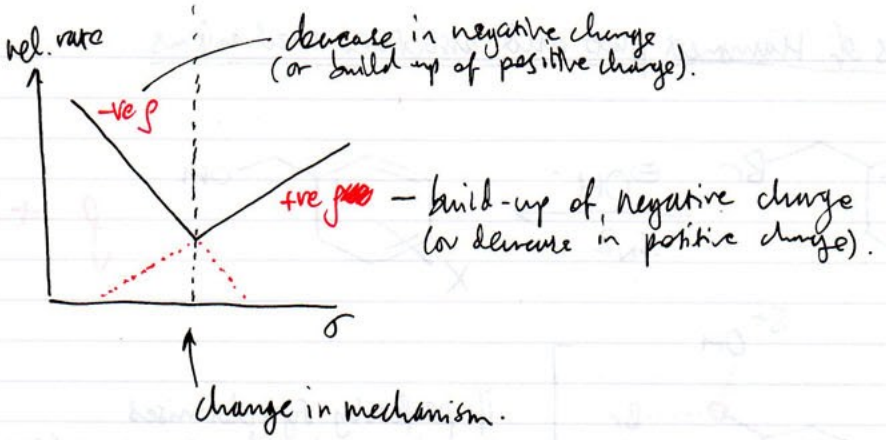


Can also use $\sigma^+ \rightarrow \rho^+$
and $\sigma^- \rightarrow \rho^-$

In "σ tables" where an entry has no σ^+ or σ^- value, use the σ value

Hammett Analysis Flow Diagram





Size of ρ

0 = no Δ charge

± 0 – 1 = very small Δ charge

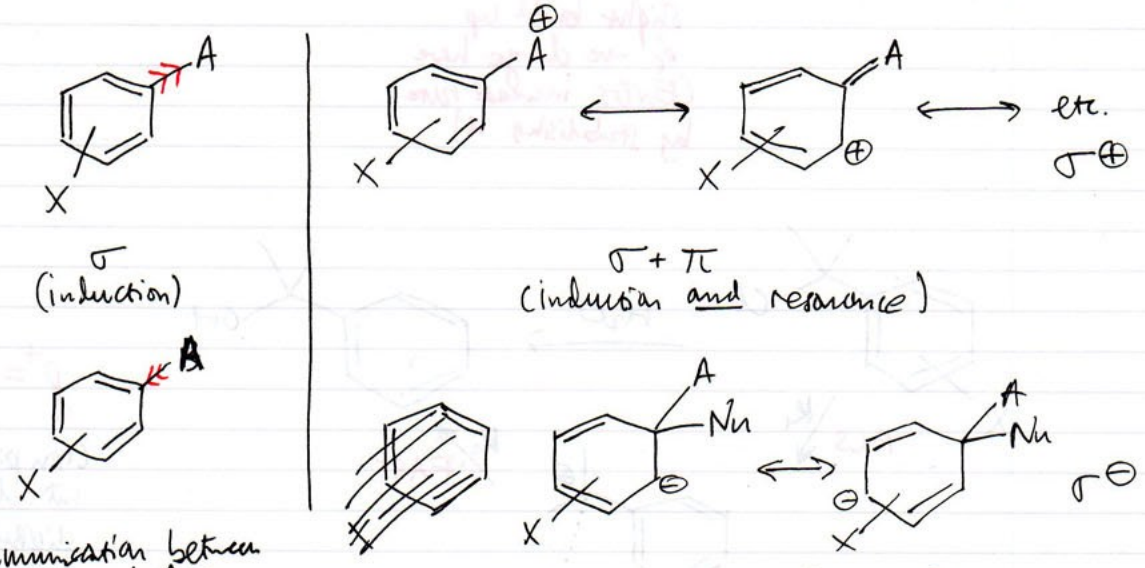
± 2 – 4 = medium to large Δ charge

± 5 – 8 = very large

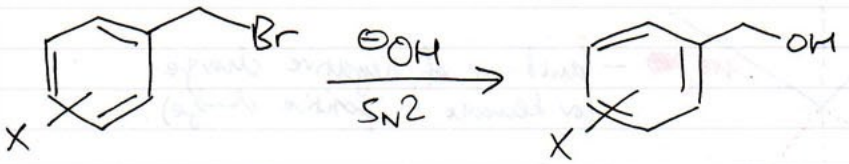
Useful way to think about size of ρ:

$$\frac{\text{rate } p\text{-NO}_2}{p\text{-MeO}} \simeq 10^{\rho}$$

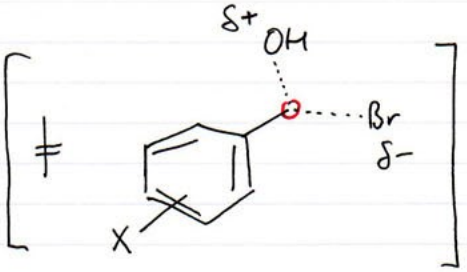
σ versus σ⁺ versus σ⁻



Examples of Hammett plots and associated mechanisms.



ρ +0.3



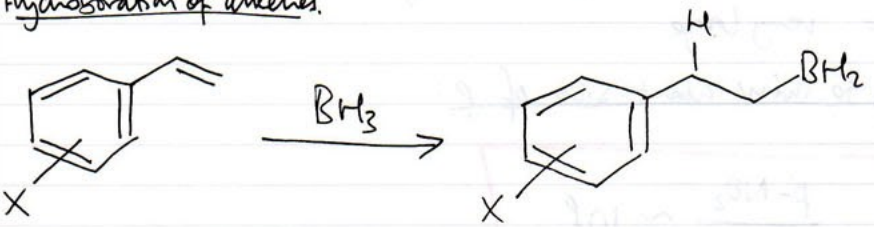
if perfectly synchronised no charge builds at carbon ($\rho = 0$)

experimentally, $\rho = +0.3$

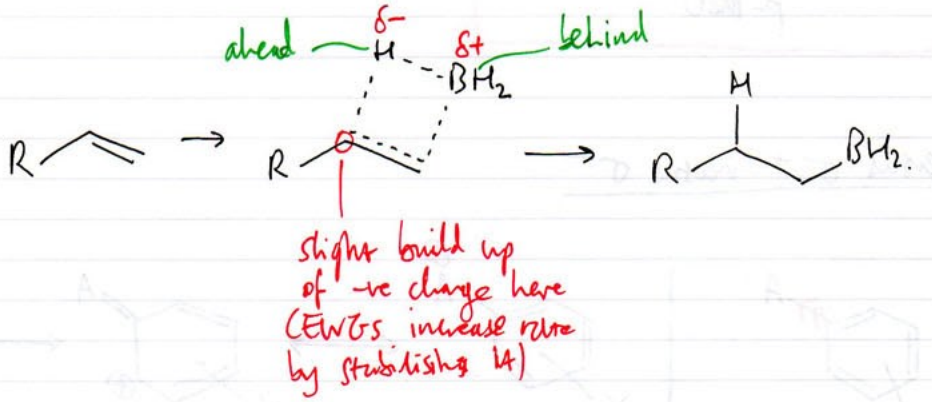
∴ slight negative charge at ≠

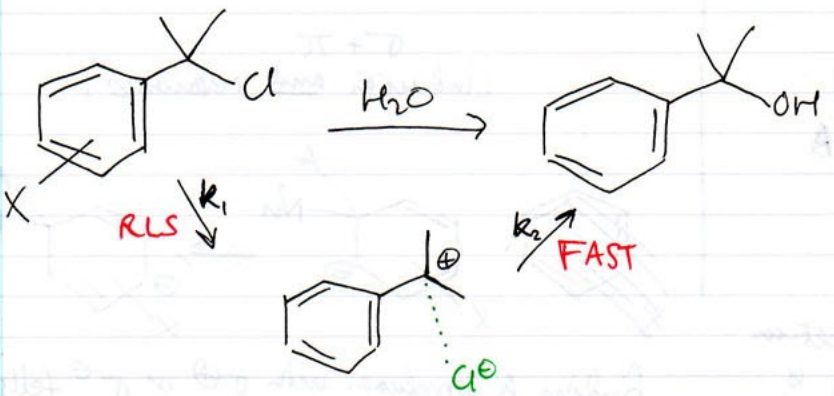
∴ $^{\ominus}OH$ begins to bond slightly before $Br^{\ominus}$ begins to leave

Hydroboration of alkenes.



ρ +0.5

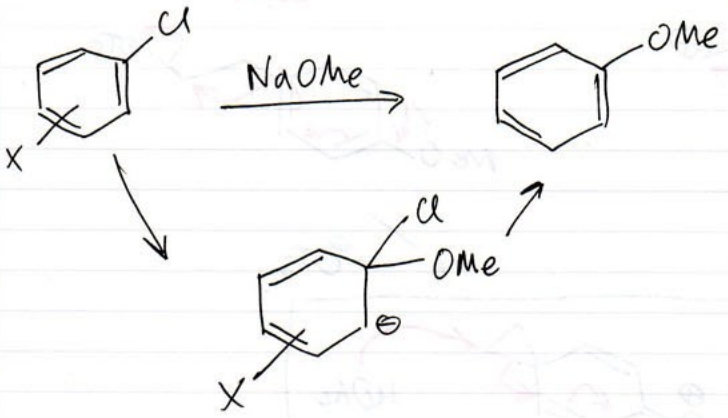




$\rho^{+} = -5.5$ (from σ^{+})

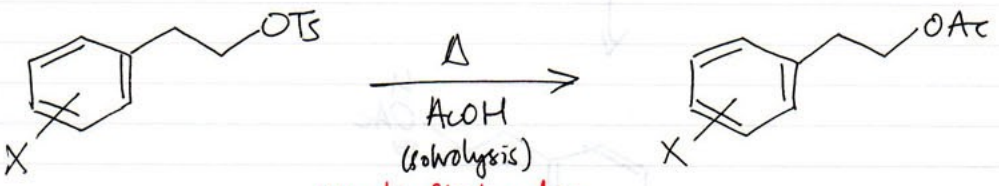
C ion pairing with chloride slightly suppressing ρ below 8)

Nucleophilic aromatic substitution

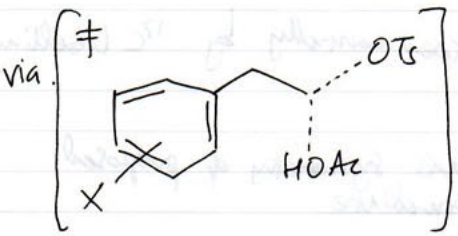


$\rho^- = +8$

full blown anionic intermediate



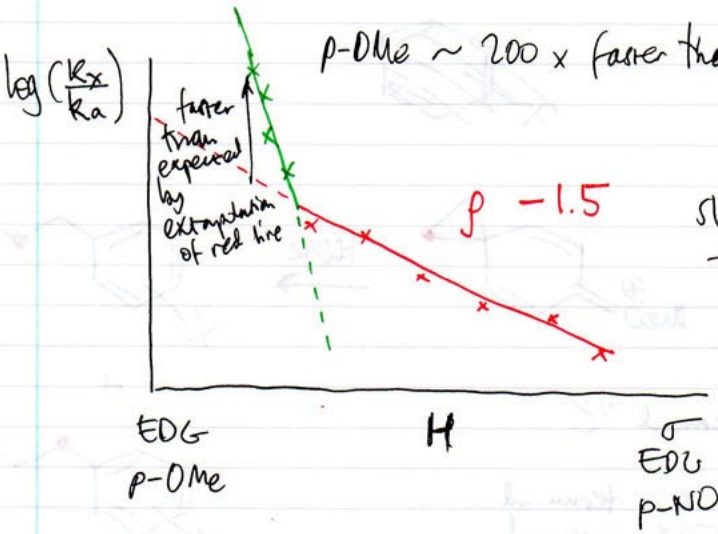
pseudo first order
(mostly) S_N2

via 

S_N2:
expect very little impact of σ of X on rate – no charge accumulation.

if perfectly synchronised, expect $\rho = 0$

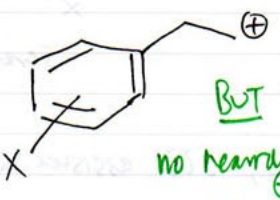
p-OMe ~ 200 x faster than predicted by $\rho - 1.5$.



Slight negative gradient
– consistent with slight positive charge building up: tosylate begins to leave slightly before AcOH fully attacks.

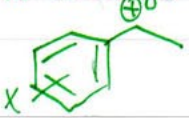
— S_N2

— different pathway with sufficiently electron donating groups more S_N1-like?

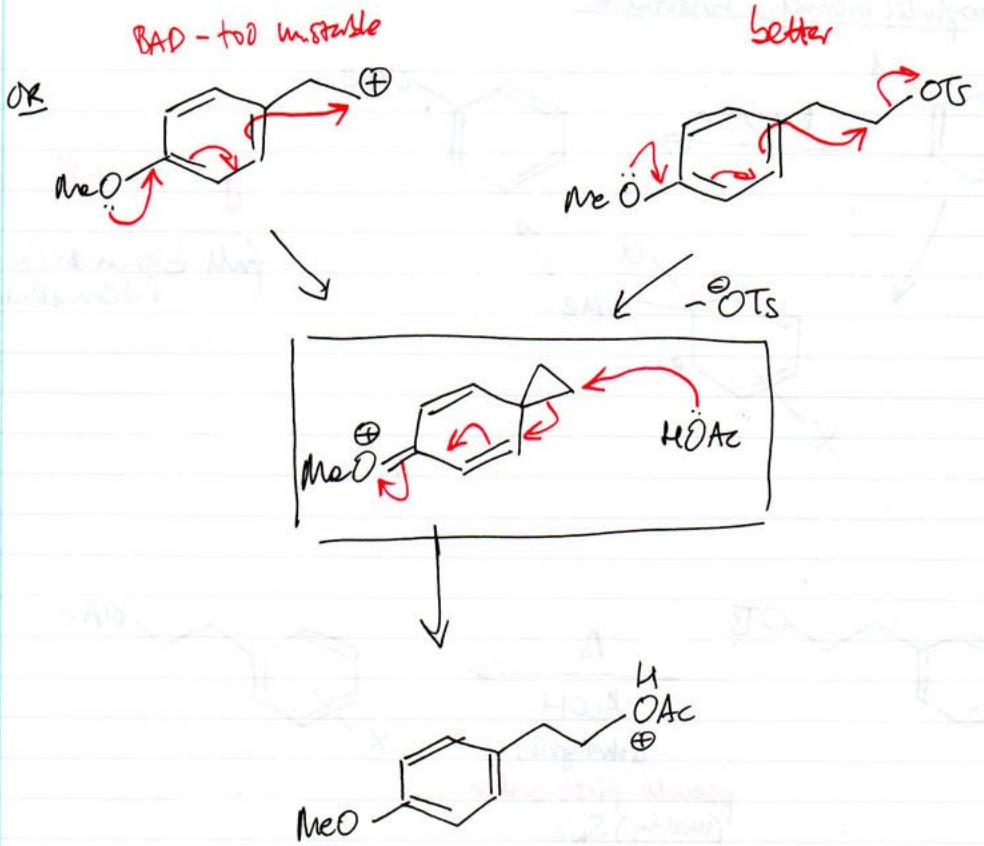


BUT 1°

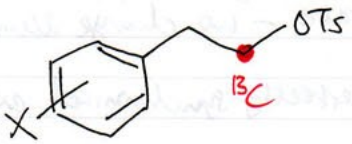
no rearrangements observed



[1,2]-H

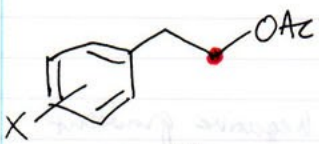


could probe these mechanisms experimentally by ^{13}C labelling:

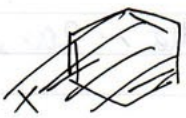


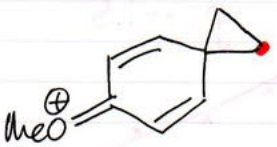
breaks symmetry of proposed intermediate

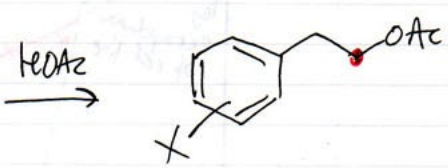
S_N2 would lead to



no scrambling.

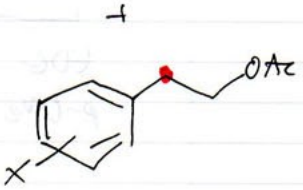






pure S_N2 gives 100% terminal ^{13}C

pure assisted S_N1 gives 50% terminal
50% internal



Scrambling.

if you found a 75:25 ratio of terminal: internal ^{13}C atoms, it'd be due to 50% S_N2, 50% assisted S_N1.

Isotopic Labelling : two uses : i) non-perturbing – using it to track atoms as an inert marker

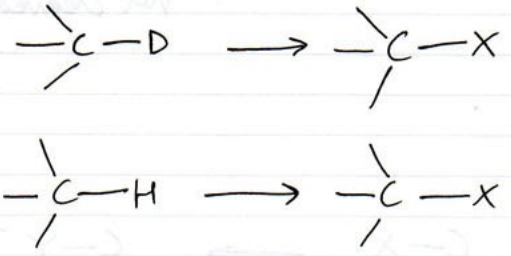
ii) kinetic effect expected or looked for – the isotope affects the reactivity.

^2H only ↓ heavier isotopes lead to much smaller effects

(a) Primary kinetic isotope effect (PKIE)
(b) Secondary kinetic isotope effect (SKIE)
- α
- β
- steric

(c) solvent KIE
(d) Tunneling – leads to enormous KIEs.

Primary KIE – where bond to the isotope is cleaved during rxn.

– e.g. 

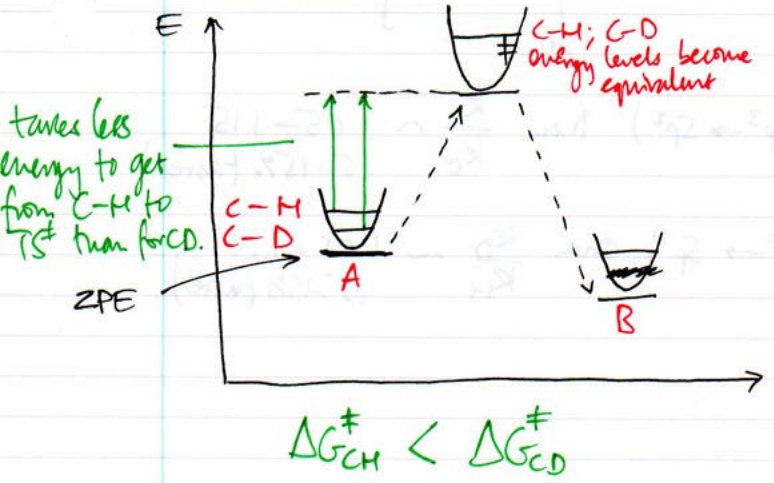
$\frac{k_H}{k_D}$ = PKIE

temperature dependent

~ 7 (maximum) at room temp. (±1)

(at lower T, KIE increases)

C–D bond is not stronger than the C–H bond but it takes more energy to break it (counterintuitive!)



$\Delta G^{\ddagger}_{CH} < \Delta G^{\ddagger}_{CD}$

lower zero point energy with D because it's heavier (simple harmonic oscillator)

C–H Z–X → [C···H···ZX]‡

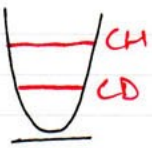
C–D Z–X

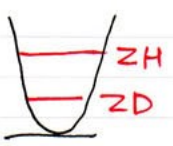
no difference in energy if perfectly symmetrical

[C···D···ZX]‡

C D–ZX.

C H–ZX

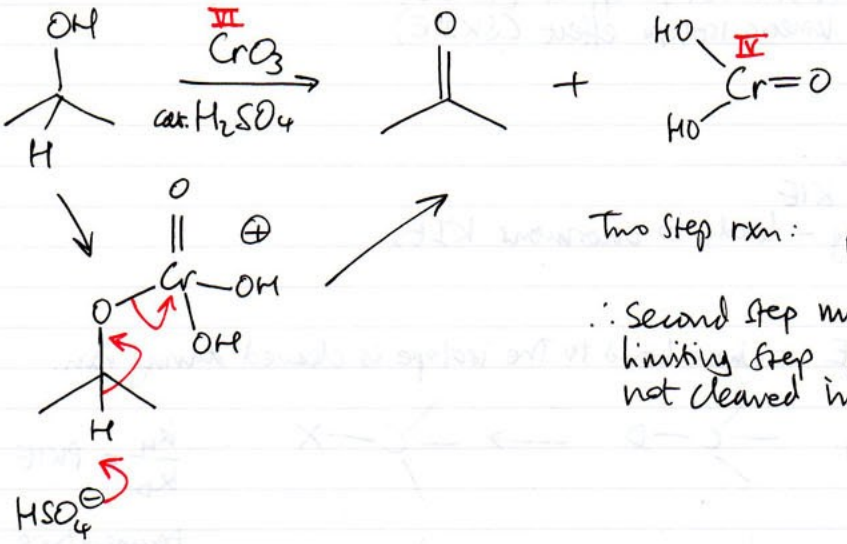




Therefore PKIE $\frac{k_H}{k_D} \sim 7$ if C–H/D is cleaved up to or including RLS.

Example of PKIE.

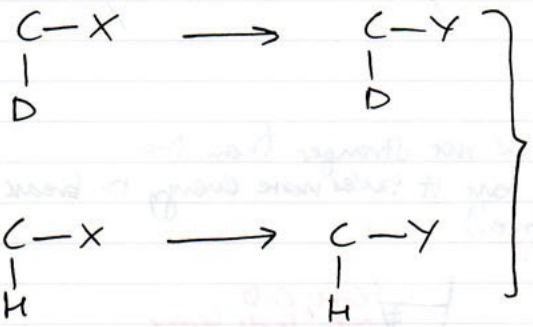
Oxidation of isopropanol with Jones' reagent.



Two step rxn: PKIE $\frac{k_H}{k_D} = 7.0$

∴ Second step must be the rate limiting step (∵ C–H/D bond not cleaved in first step)

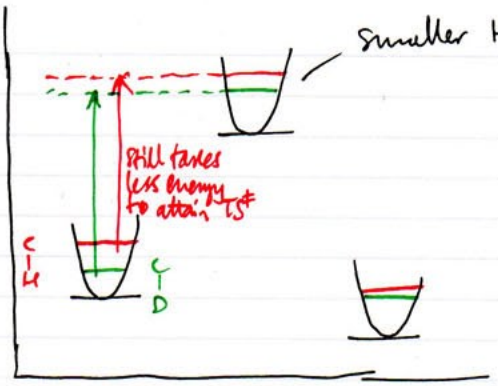
α-SKIE:



$\frac{k_H}{k_D}$ depends on change in hybridisation at carbon

p character ↓ (eg. $sp^3 \rightarrow sp^2$) then $\frac{k_H}{k_D} \sim 1.05-1.15$ (5–15% faster)

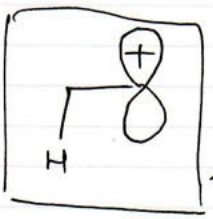
p character ↑ (eg. $sp^2 \rightarrow sp^3$) then $\frac{k_D}{k_H} \sim 1.05-1.15$ (5–15% faster).



β-SKIE – useful for carbocation detection – hyperconjugation.

D–C is slightly shorter than H–C

poorer overlap due to shorter C–D bond

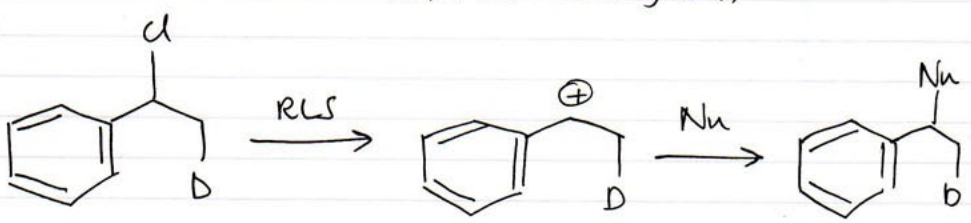


– has to be planar

∴ SKIE $\frac{k_H}{k_D} \sim 1.15 \rightarrow 1.25$

(providing you're generating a carbocation in the rate limiting step)

eg. S_N1



$\frac{k_H}{k_D} \sim 1.15 - 1.25$