# CHEM 30B – ORGANIC CHEMISTRY LEC#1
## Reactivity & Synthesis I

(1) WHO / WHEN / WHERE / HOW ?
(2) CNSI SEMINARS / EXTRA CREDIT
(3) ORGANIC SYNTHESIS

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(1) SYLLABUS

- 3077D YH, Office Hours 3-4 pm T,R (3077F)
- VOH → 30B Fall – practice problems.
- TAs ROB / MIKE OH ?
- DISCUSSION D, G, I cancelled
- EXAMS (QUIZZES MULTIPLE CHOICE)
  10 Questions + 1 BONUS Question
  MIDTERMS → PRIZES
- GRADES / REGRADES / IMPACTED / CHEATING!
- ENGLISH ENGLISH → ALUMINIUM / Z etc

(2) CNSI seminars
CS50 Tuesdays 5pm
- Learn something new and...
EXTRA CREDIT

250 word summary, 1 week after seminar
→ 10 points, you can do TWO.

→ EXPLAIN HOW IT GETS ADDED IN...
MORE THAN 1/2 CLASS GOT BETTER GRADE LAST TIME.

ALTERNATIVES if you can't attend.

— RADICALS
ORGANIC
(3) SYNTHESIS

Why? → Medicines / Materials

CRUDE OIL ⇒ BUILDING BLOCKS
What if we need larger more complex molecules?

Some complex molecules come from natural sources
→ Mother Nature does the synthesis
- might not be enough
- structural analogs

SYNTHESIS - underpins most of ORGANIC CHEMISTRY
= make a molecule before studying it...

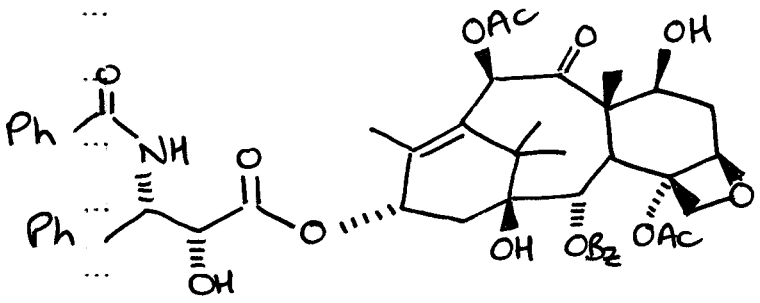
... First molecule drawn on board –

...

... start simple ⟹ TAXOL

...

...




...

... most promising anti-tumour agent developed
... in the last three decades

...

... 1998 Sales $1.2 BILLION

...

... Where from?
... Not like something like this grass on trees!

...

... Well, YES it does.
... – BARK of PACIFIC YEW TREE

...

... six 100yr old trees to treat one patient
... → kills trees.

...

... Let's make it using chemical synthesis
... > 40 steps, < 2% yield

...

...

# - RETROSYNTHETIC ANALYSIS

Let's say 26 steps

A —rxn→ B —rxn→ C —rxn→ D → → → Y → Z → TAXOL

↑

commercially available small molecule

VERY DIFFICULT / IMPOSSIBLE to plan making TAXOL this way.

ARROW ⟹

RETROSYNTHESIS

TAXOL —rxn→ Z —rxn→ Y ⟹ X ⟹ ⟹ ⟹ B ⟹ A

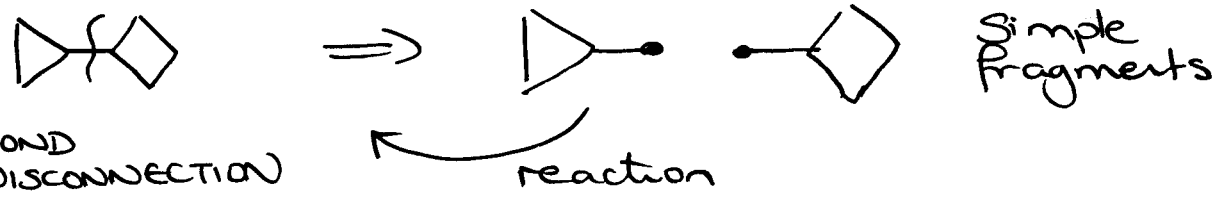
↑

a slightly more simple structure that we can convert into TAXOL using a reaction we know

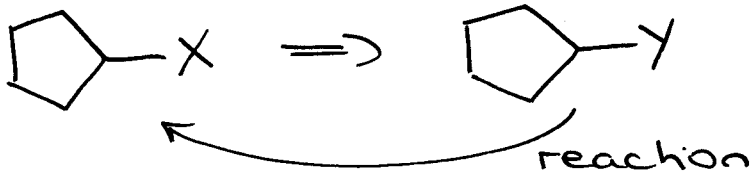
- SIMPLIFY molecule STEP by STEP
- Each RETRO step must correspond to a real reaction in reverse

TWO TYPES OF RETROSYNTHETIC STEP

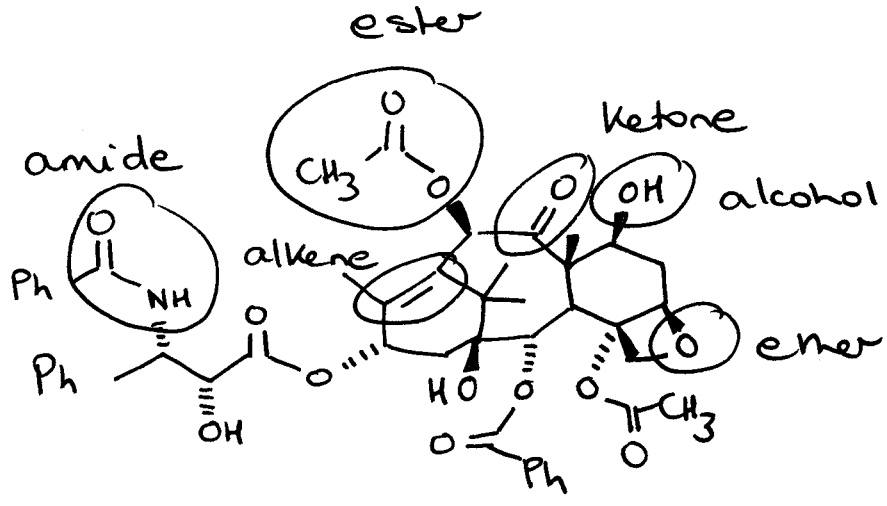
(i) DISCONNECTION



(ii) FUNCTIONAL GROUP INTERCONVERSION (FGI)




- You need to know reactions
- You need to know spectroscopy to characterize the products of reactions




So how is TAXOL made — semisynthesis

Needles of English Yew Tree (does not kill tree) → advanced intermediate A→Z

4 steps (> 80% yield.)

# CHEM 30B – Lecture 3

1. ALCOHOL ACTIVATION
2. ACID CATALYZED DEHYDRATION
3. PINACOL REARRANGEMENT
4. OXIDATION

(3 & 4) NOT TODAY

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Homework 9.30 – 9.39

## 1. ACTIVATION

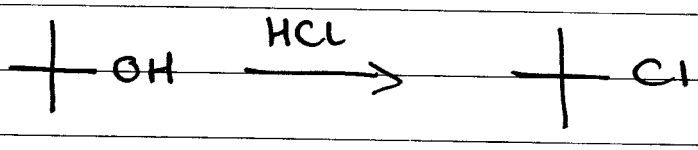
$$R\text{–}OH + Nuc \longrightarrow R\text{–}Nuc + OH^-$$

($OH^-$: not a good LG)

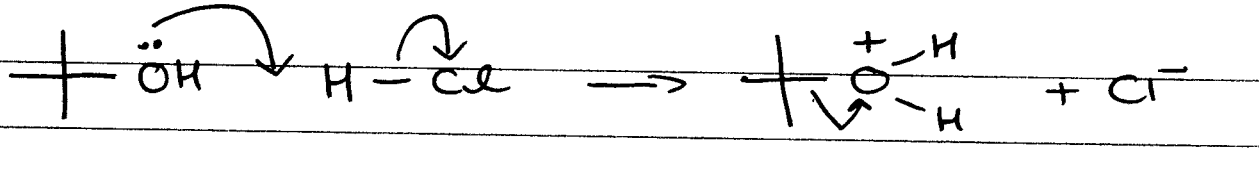
activate OH, turn into good LG

### (i) ALKYL HALIDES (rxn HCl/HBr)

$3^\circ$ alcohols – rapid at rt

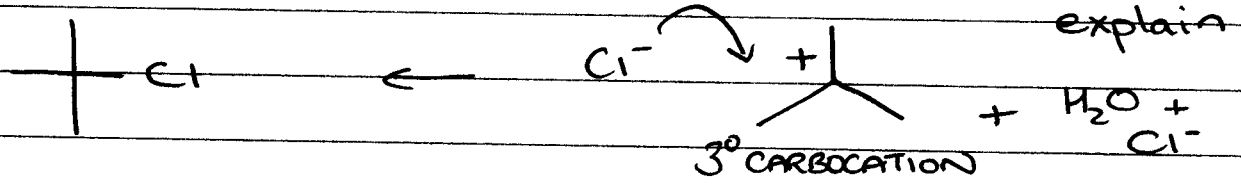


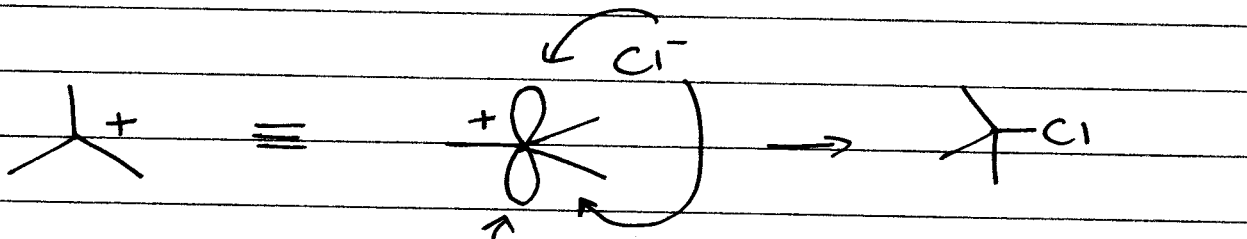

HOW DOES THIS WORK? – MECHANISM

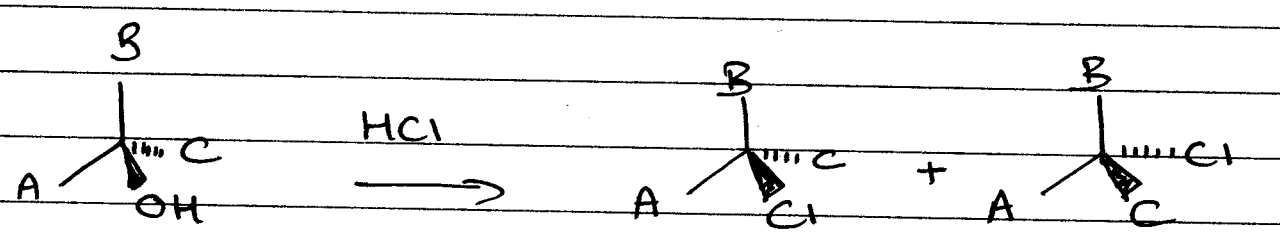


RDS ($S_N1$)

explain




ENANTIOMERICALLY PURE

RACEMIC MIXTURE

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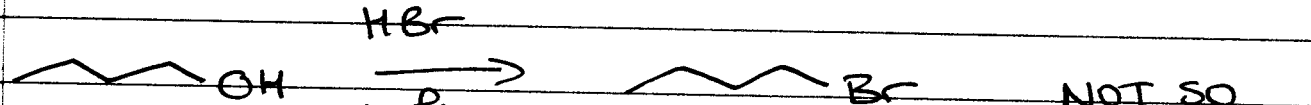
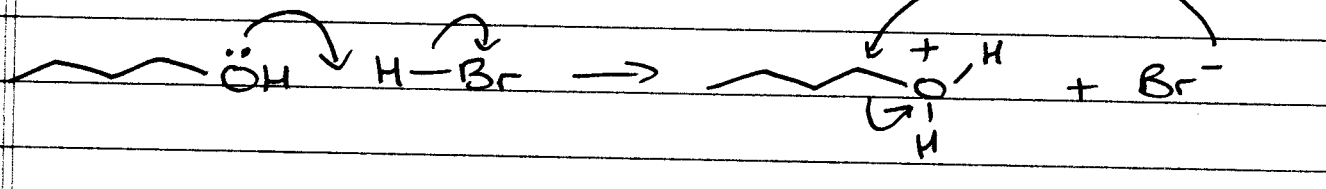
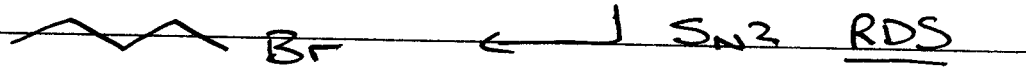
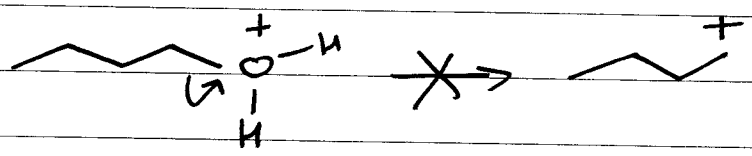
1° ALCOHOLS



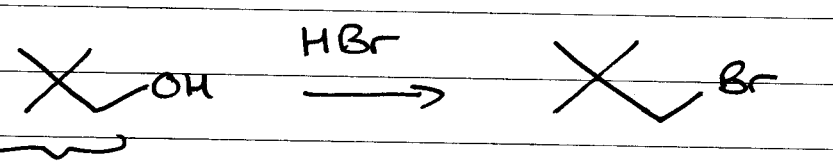

NOT SO HINDERED



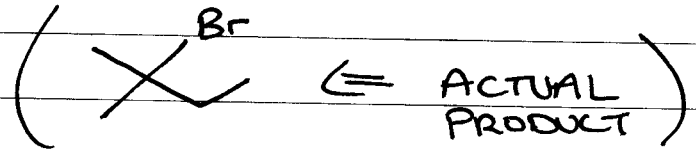


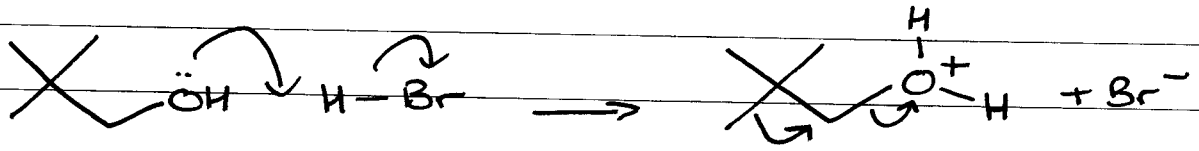



## BRANCHED 1° ALCOHOL




neopentyl

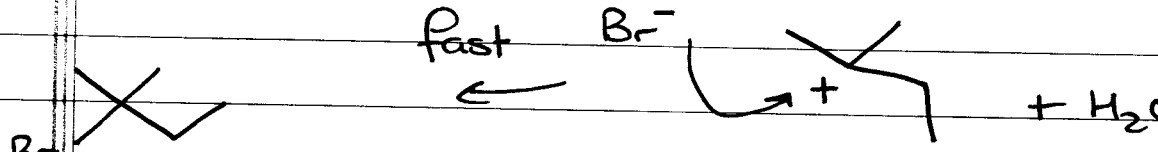


$S_N1$ like

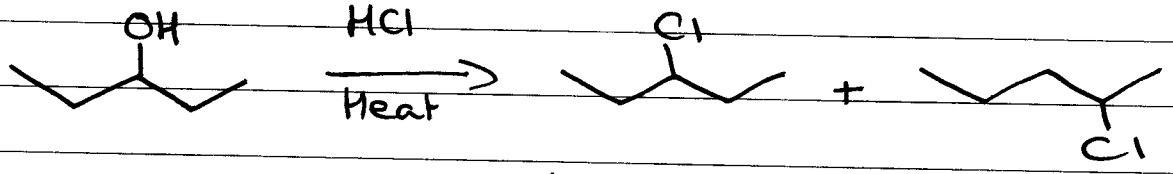
RDS concerted

ALKYL MIGRATION




3° carbocation

## 2° ALCOHOLS



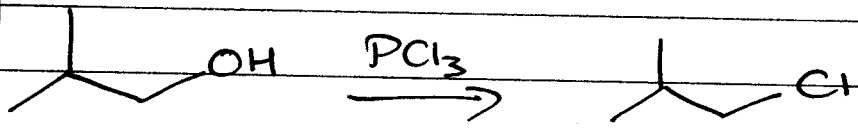

$S_N1$, $S_N2$, BOTH! ($S_N1$ = REARRANGEMENT)

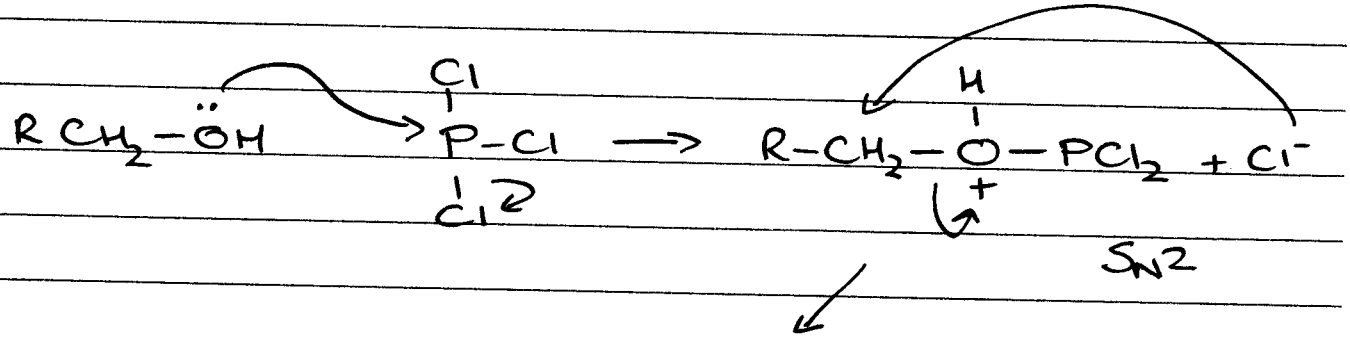
In summary

Good rxn for 3° ROH and v simple straight chain 1° ROH

- So how do we deal w/ 1° and 2°

use $PX_3$ X = Cl, Br (milder reagent less rearrangement)

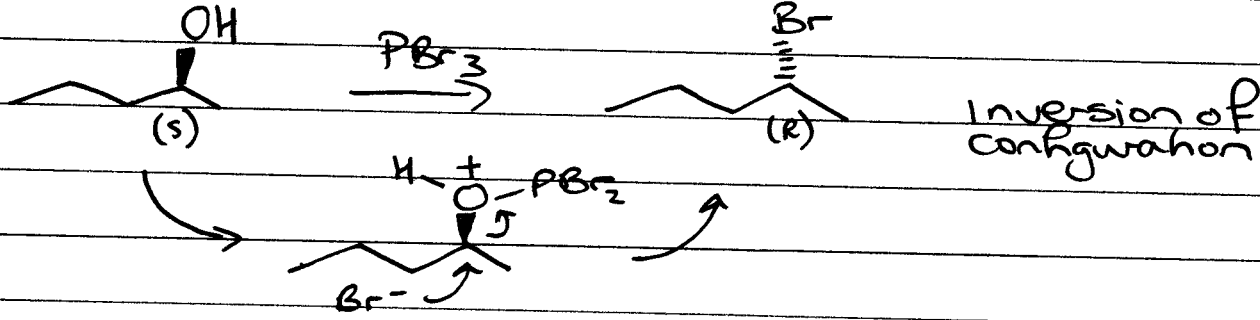


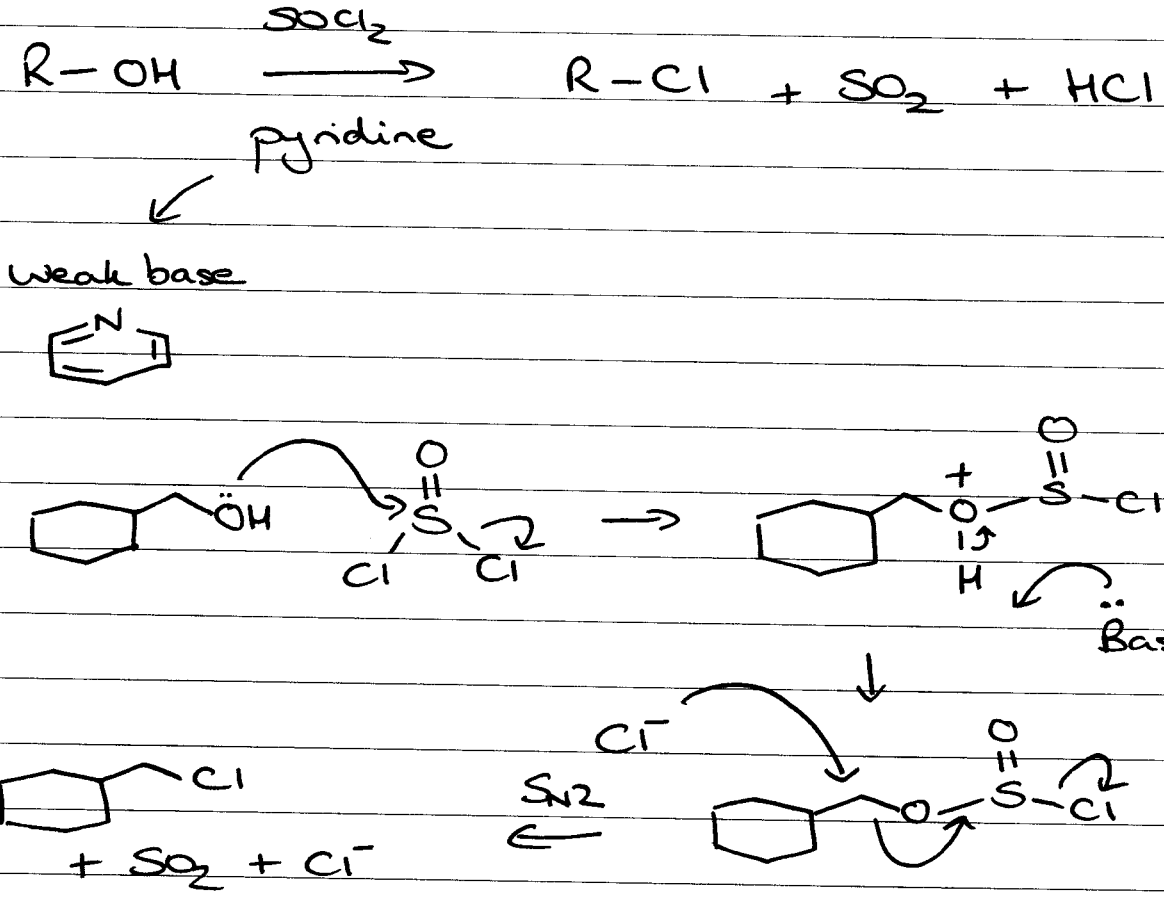

$RCH_2Cl$ + $PCl_2OH$ (still reactive)

$H_3PO_3$

phosphorous acid



$SOCl_2$

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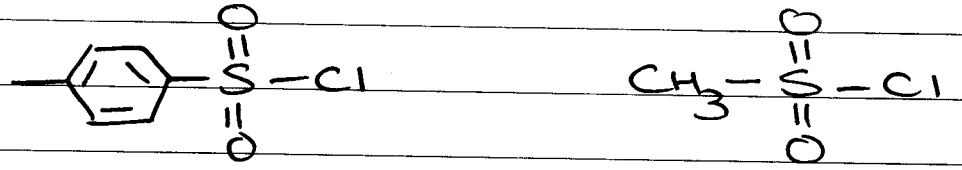
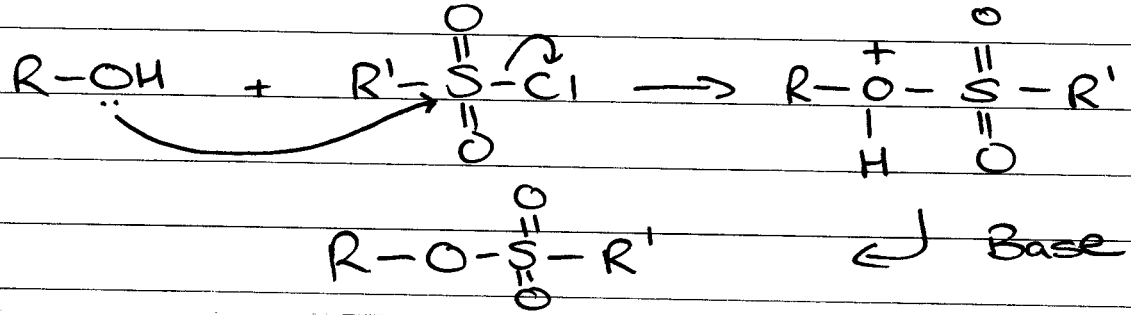
SULFONYL CHLORIDES

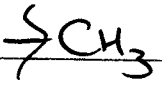


Tosyl chloride
TsCl

Mesyl chloride
MsCl

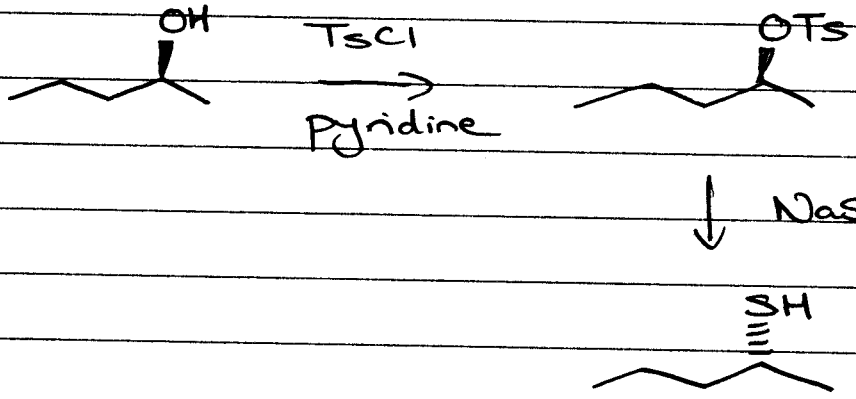


$R^1$ =  = R-OTs tosylate

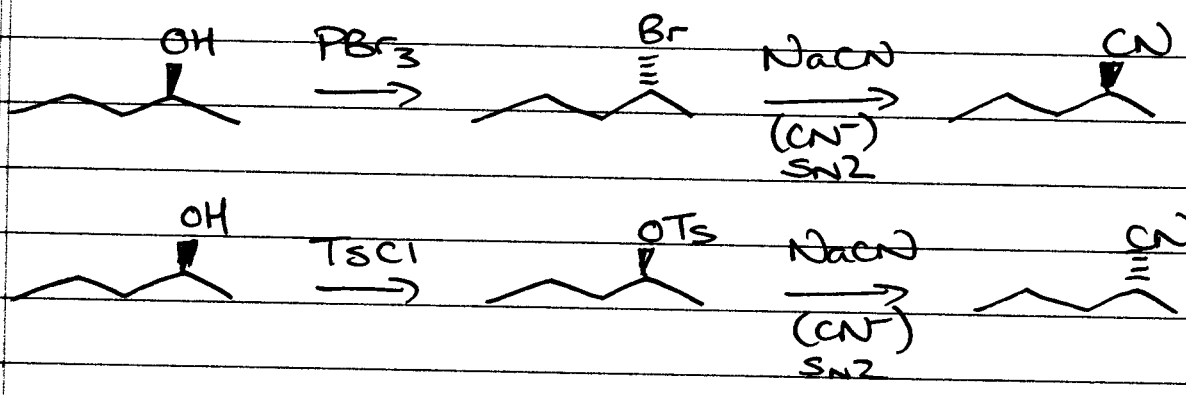
$R^1$ =  = R-OMs mesylate

ALKYL SULFONATES

RETENTION of CONFIGURATION




So:




RETRO:

R-CN ⇒ R-Br or R-OTs ⇒ R-OH

... DEHYDRATION)

Lec (4)

(1) DEHYDRATION
(2) PINACOL REARRANGEMENT
(3) OXIDATION

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(1) QUIZ ON WEDNESDAY 10 am SHARP
(2) CNSI Lecture
JERRY ATWOOD – "SYNTHESIS AND APPLICATIONS OF MOLECULAR CAPSULES"

CS50 5pm
(3) HMK 9.10-9.13, 9.30-9.32, 9.36-9.39, 9.41

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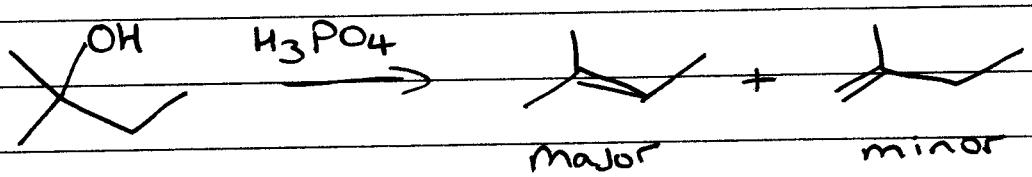
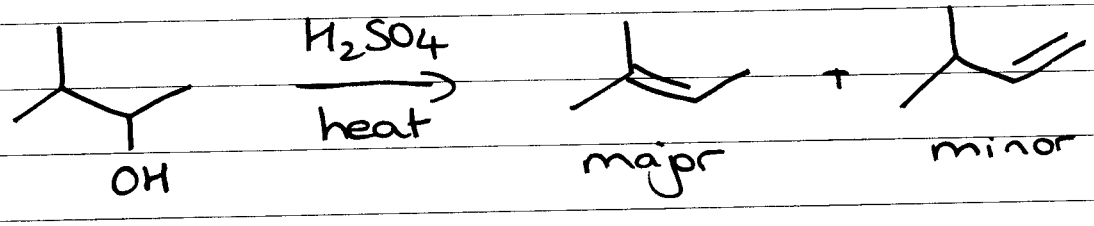
(1) DEHYDRATION
3° ALCOHOL




ZAITSEV RULE

# 2° ALCOHOLS

(i)

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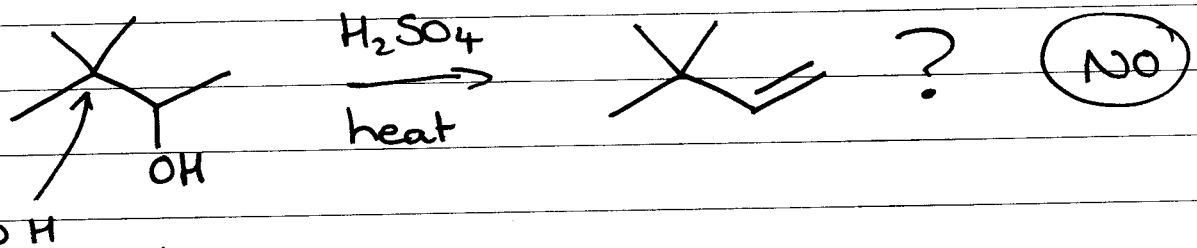
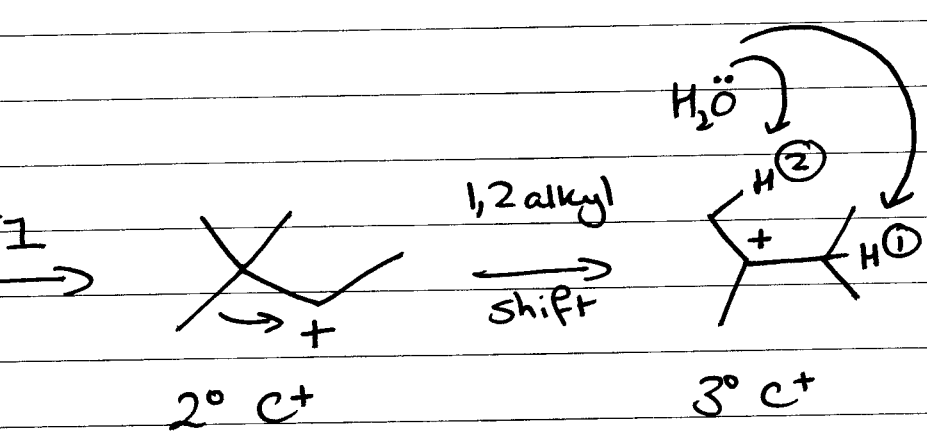
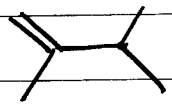


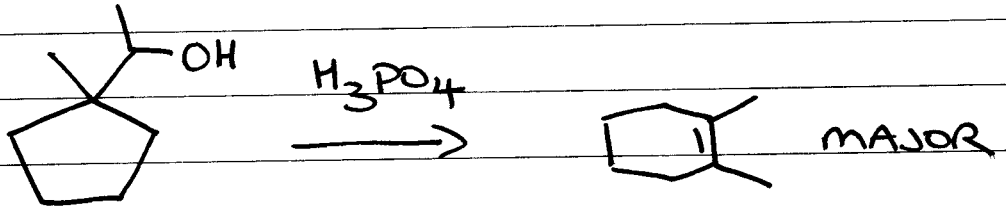

no H here

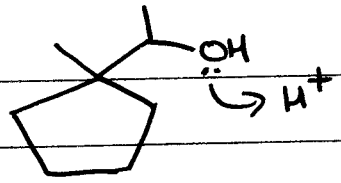


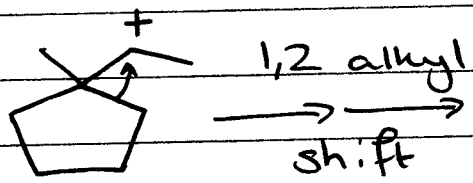

(1)  MAJOR — 4R GROUPS

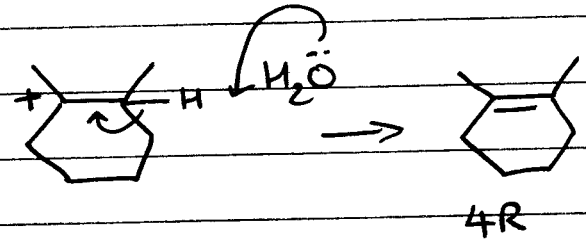
(2)  MINOR — 2R GROUPS

(iii)

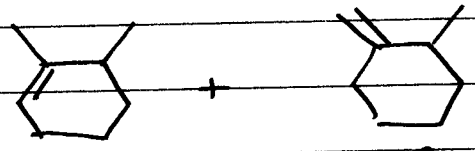




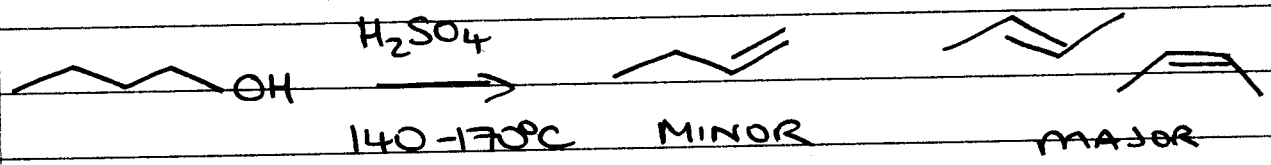



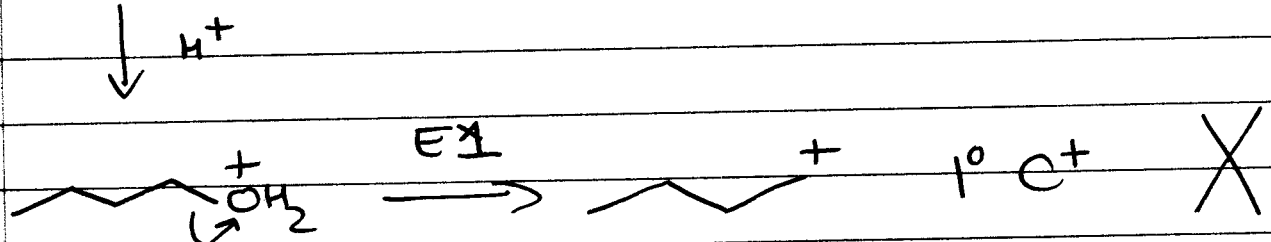



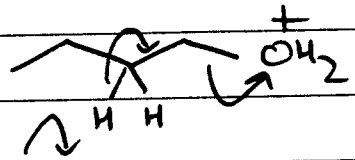

MINOR

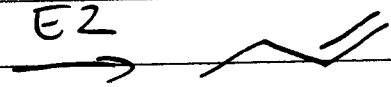


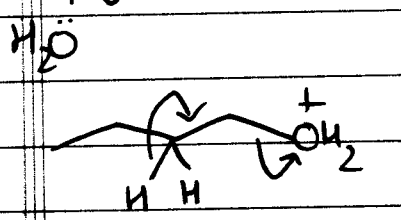

## 1° ALCOHOLS

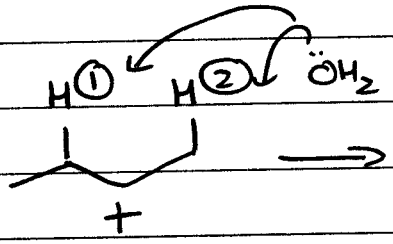


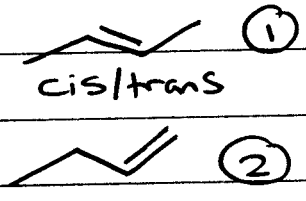



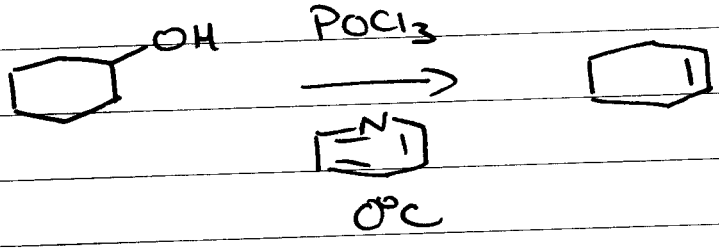



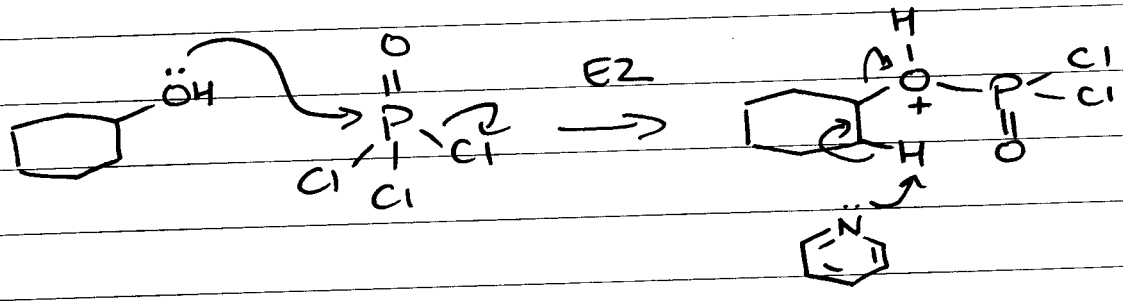



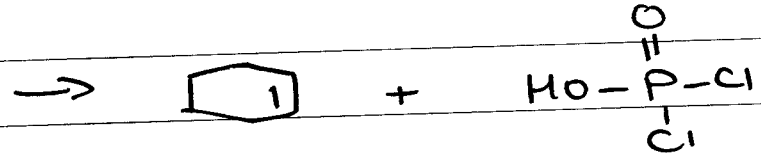



MILDER METHOD

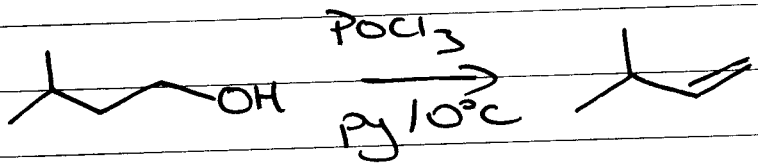
2°



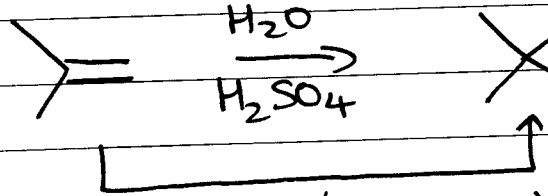

1°




DEHYDRATE ALCOHOLS ⟶ ALKENES

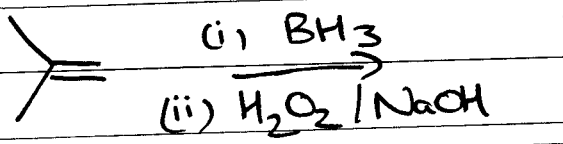
HYDRATE ALKENES ⟶ ALCOHOLS

ALKENE + $H_2O$ ⇌ ALCOHOL



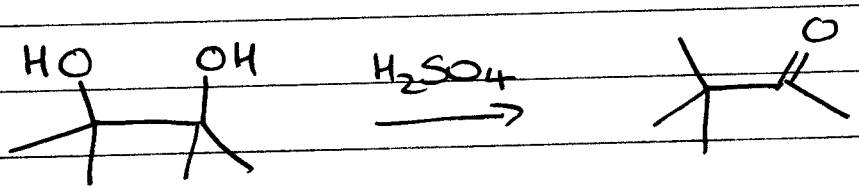

MARKOVNIKOV

(i) $Hg(OAc)_2/H_2O$ (ii) $NaBH_4$



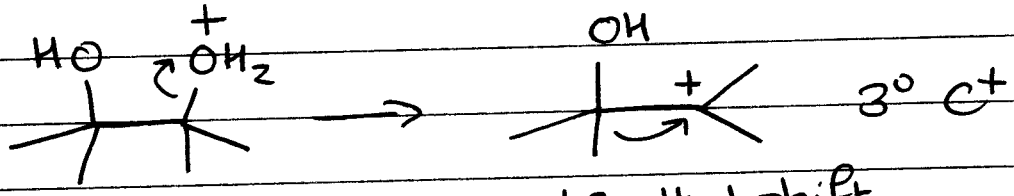

ANTI MARKOVNIKOV

## (2) PINACOL REARRANGEMENT

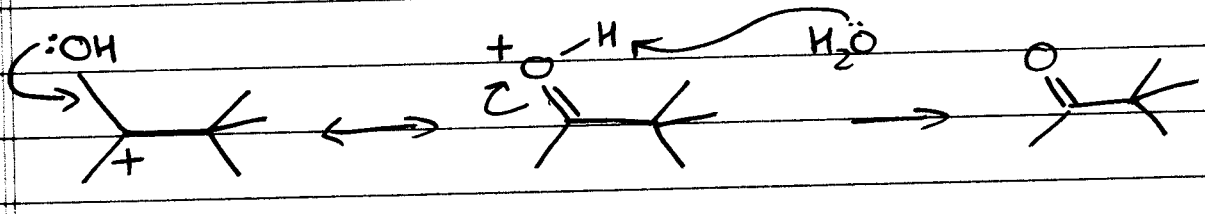




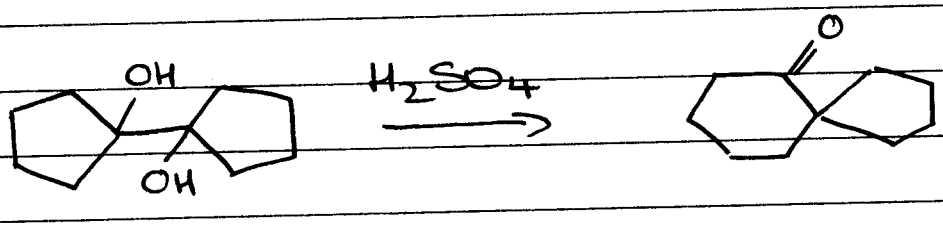





1,2 alkyl shift

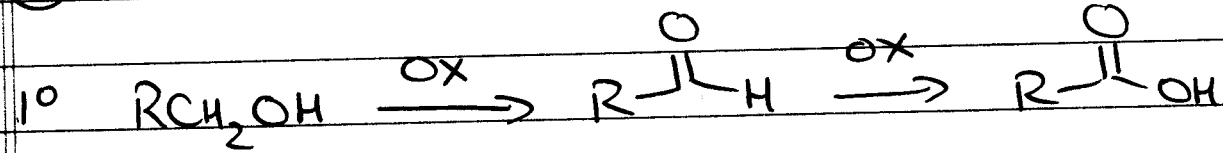



General for all 1,2 DIOLS




WORK THROUGH THIS ONE

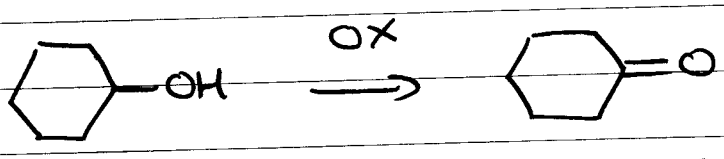
## (3) OXIDATION




ALDEHYDE

CARBOXYLIC ACID

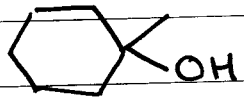
2°




STOPS HERE

KETONE

3°

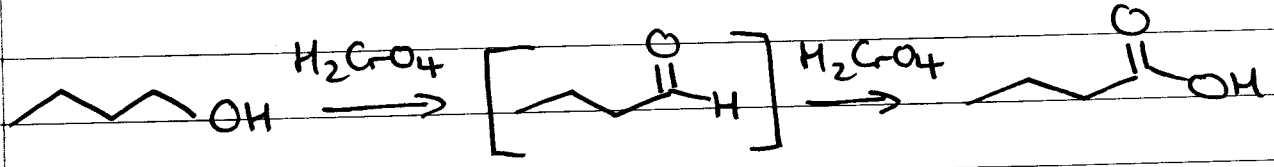



NO REACTION

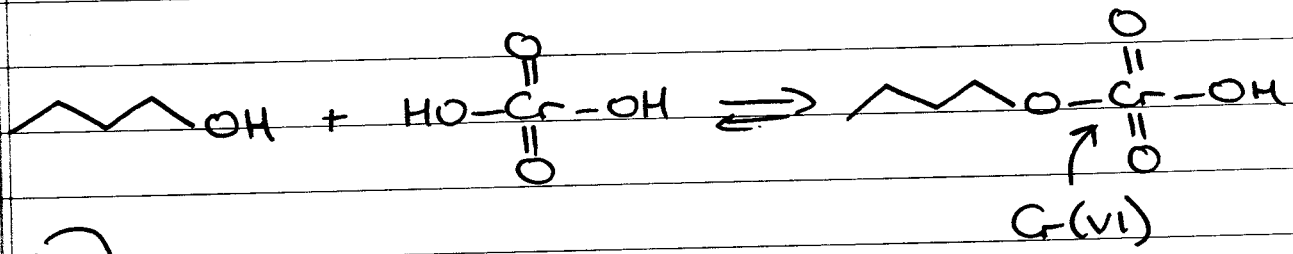
CHROMIC ACID $H_2CrO_4$

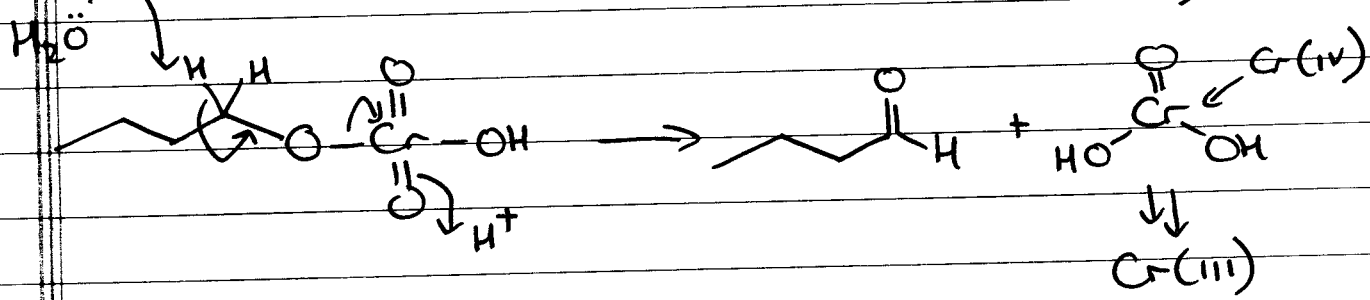
$$CrO_3 \xrightarrow[H_2SO_4]{H_2O} H_2CrO_4$$

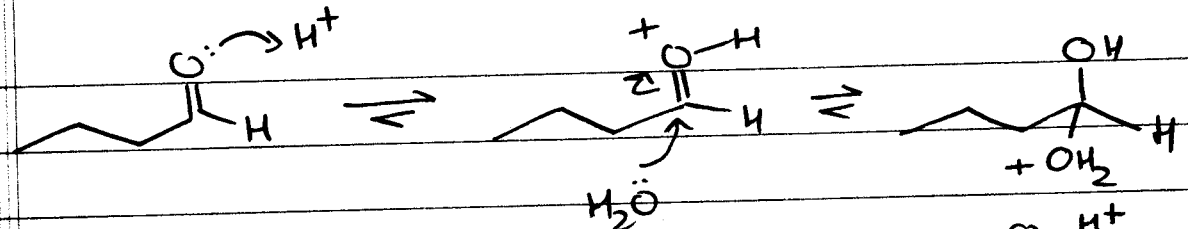
$$K_2Cr_2O_7 \xrightarrow[H_2SO_4]{H_2O} H_2CrO_4$$

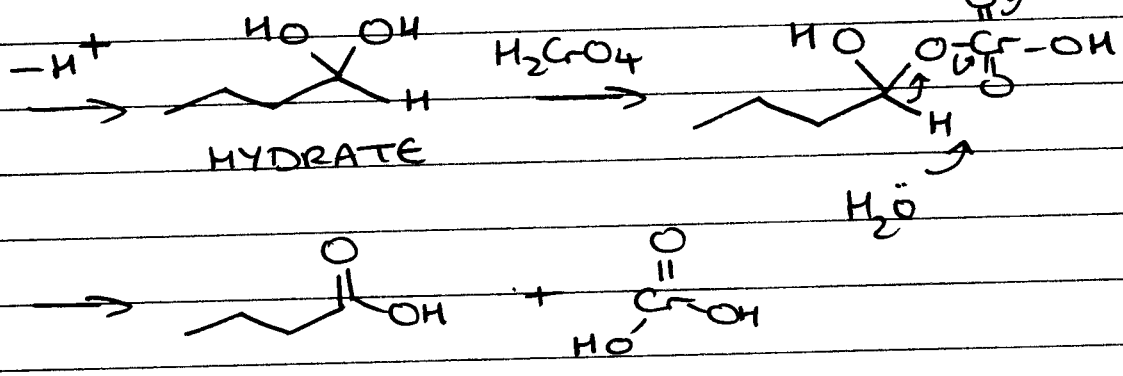



DOES NOT STOP

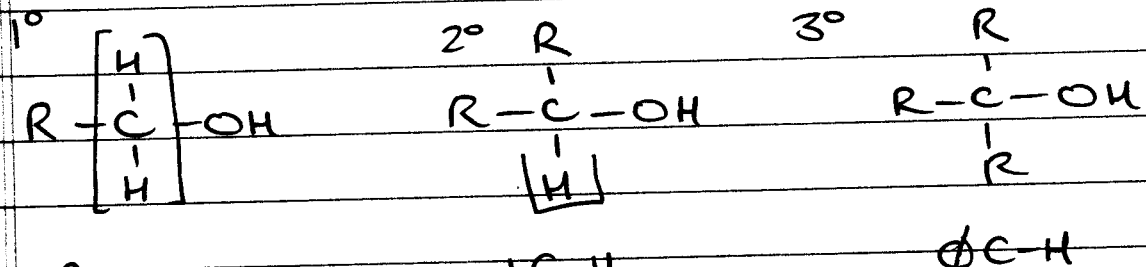






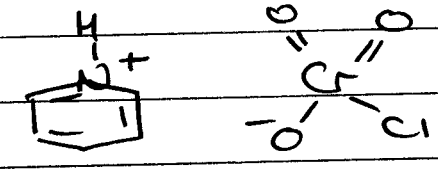


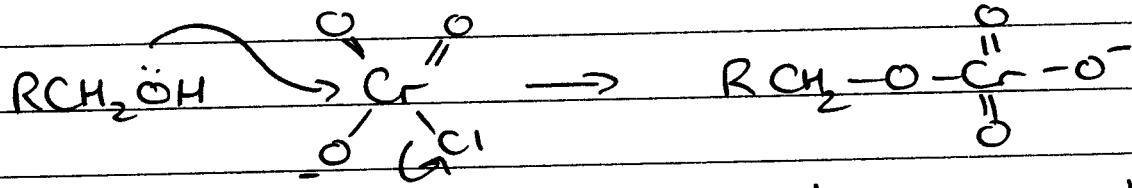




$RCH_2OH \longrightarrow RCHO \leftarrow$ STOP?

$CrO_3 + HCl +$  $\longrightarrow$ PCC

PYRIDINIUM CHLOROCHROMATE
SELECTIVE / MILD



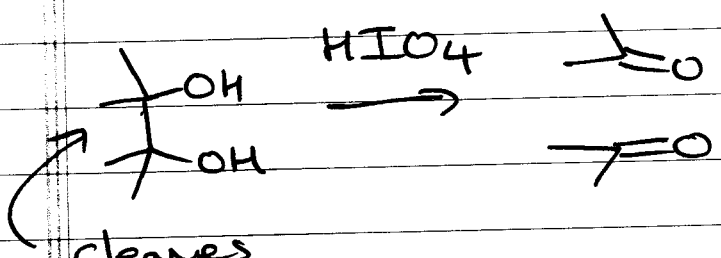


(NO WATER, ORGANIC SOLVENT)

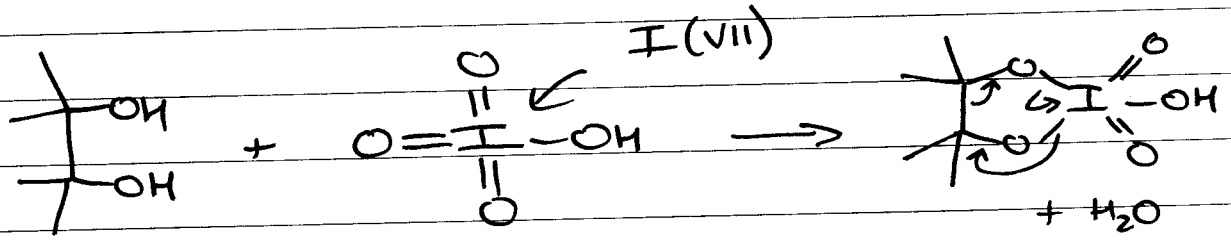
chromate ester
↓
DOES NOT FORM HYDRATE $\Longrightarrow$ aldehyde

PCC works for 2° ROH too.

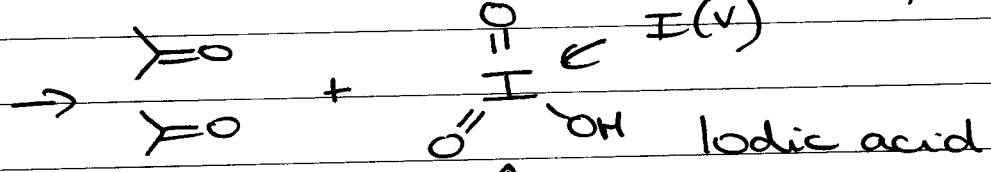
- PERIODIC ACID → $HIO_4$
  1,2 DIOLS (GLYCOLS)




cleaves bond & oxidizes




periodic ester

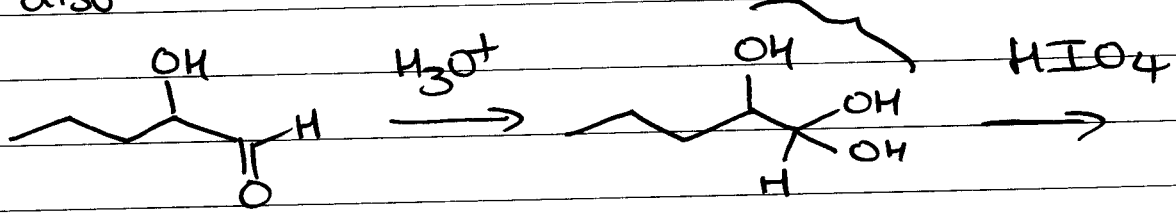


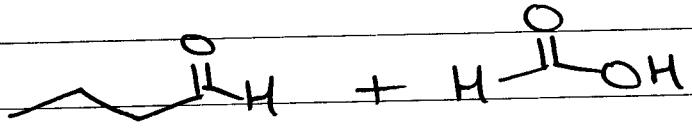

Iodic acid

↑ reduced.

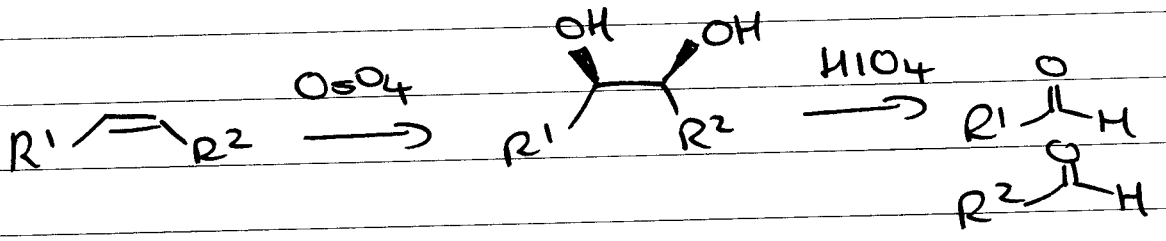
MUST BE ABLE TO FORM 5-MEM RING

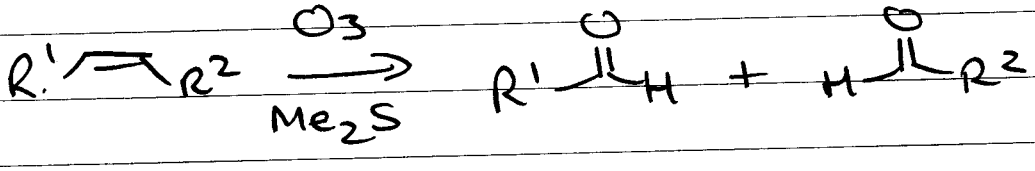
- also



# Recall Alkenes



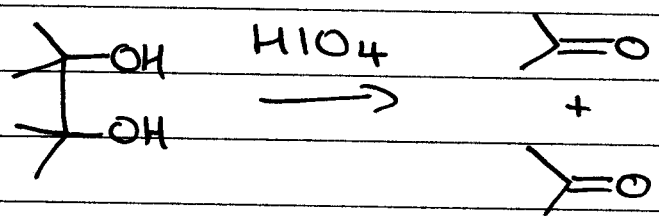
# LEC (5)

1. OXIDATION cont
2. SULFUR ANALOGS – THIOLS
   - (i) nomenclature
   - (ii) physical properties
   - (iii) preparation
   - (iv) acidity/basicity
   - (v) oxidation
   - (vi) reaction

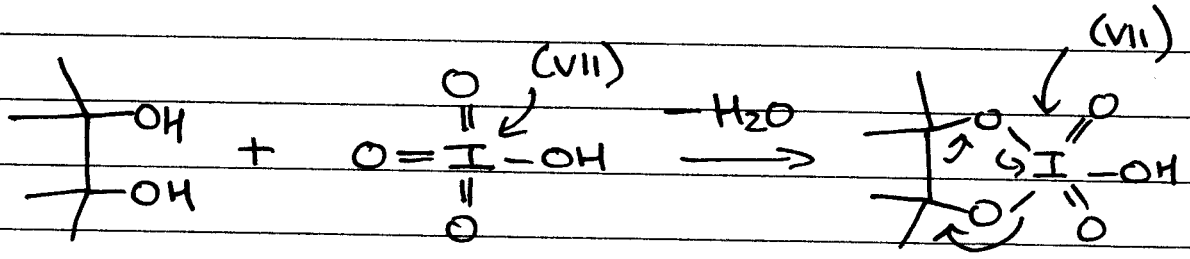
HMK Ch9.1 → Try 'em all

---

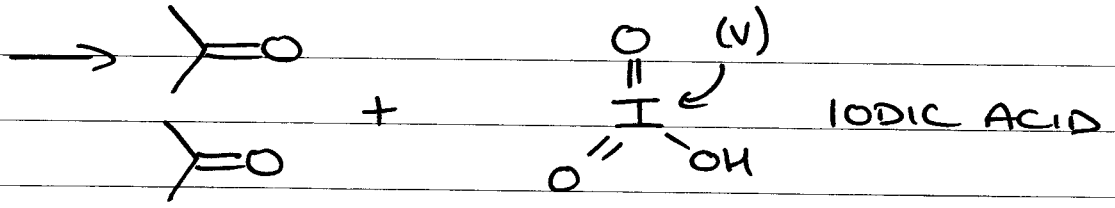
## (1) PERIODIC ACID



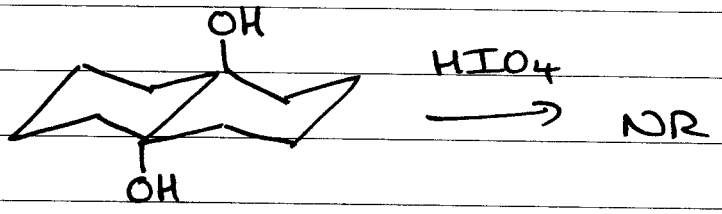

MECHANISM




CYCLIC PERIODIC ESTER

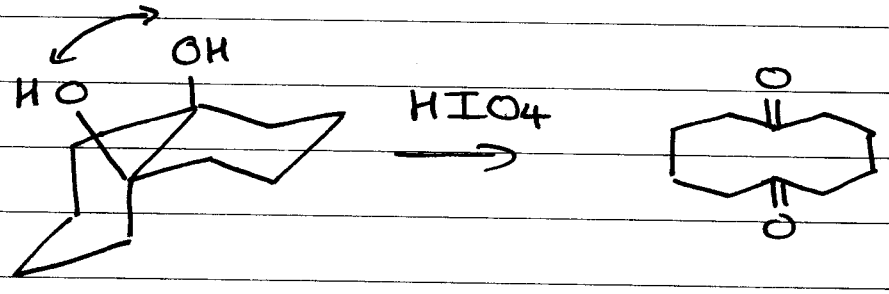



① MUST BE ABLE TO FORM 5-MEM RING



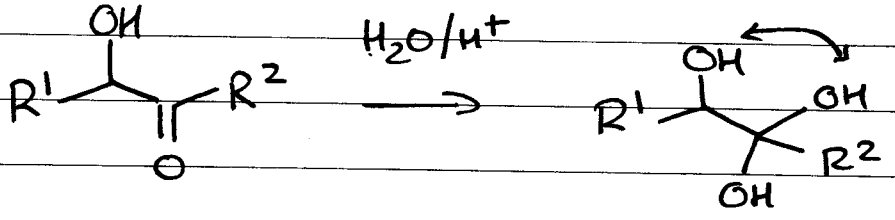

↖ locked 180° apart

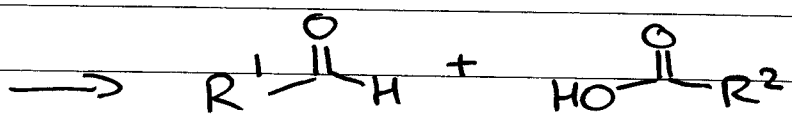
TRANSDECALINDIOL



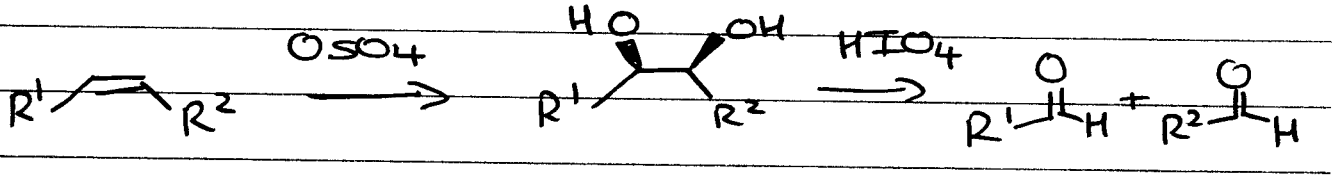

CISDECALINDIOL

α-HYDROXYALDEHYDES/KETONES ALSO REACT (via hydrate)

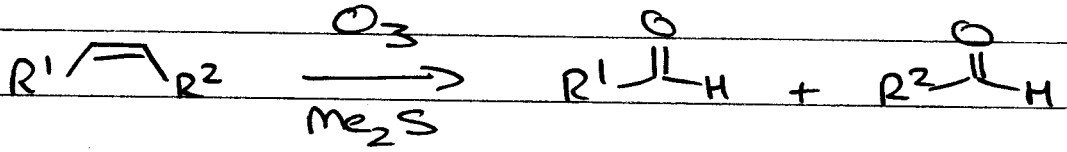


## RECALL ALKENES




(DIHYDROXYLATION)




(OZONOLYSIS)

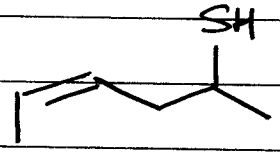
## (2) SULFUR

### (i) NOMENCLATURE

R–SH Thiol

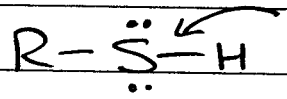
$CH_3SH$ methanethiol

$CH_3CH_2SH$ ethanethiol




(Z)-4-hexene-2-thiol

### (ii) PHYSICAL PROPERTIES

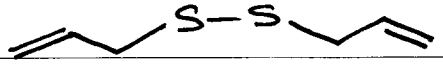



⇒ NO H BONDING

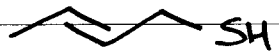
$CH_3CH_2SH$ bp 35°C
$CH_3SCH_3$ bp 37°C
DIMETHYL SULFIDE

} compare to oxygen analogs

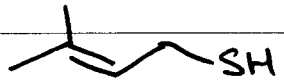
SMELL!!



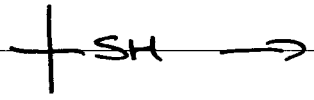
A GARLIC (DISULFIDE)



SKUNK

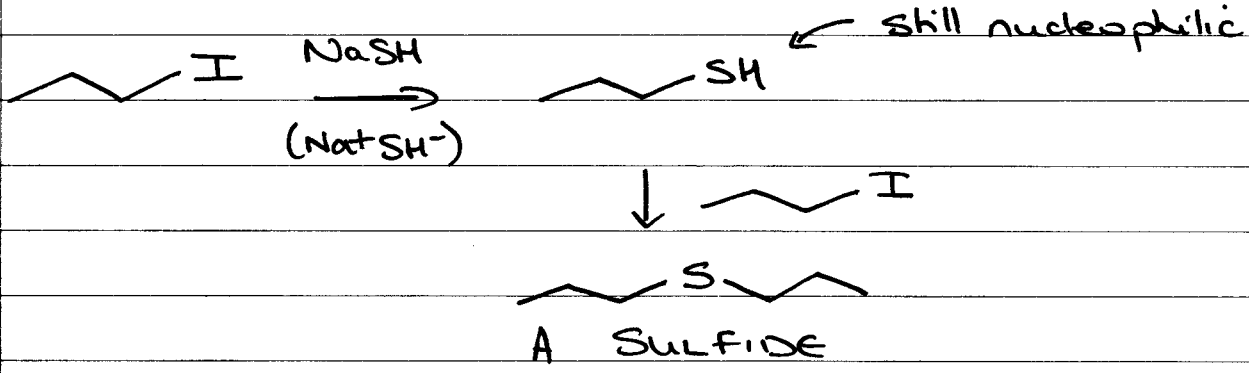


BEER (< 10ng/l) can be detected by humans.



→ added to natural gas
→ gas leaks
detect 1 part in 50 BILLION

(iii) PREPARATION



## (iv) ACIDITY / BASICITY

pka

$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+$ 15.9

$CH_3CH_2SH + H_2O \rightleftharpoons CH_3CH_2S^- + H_3O^+$ 8.5

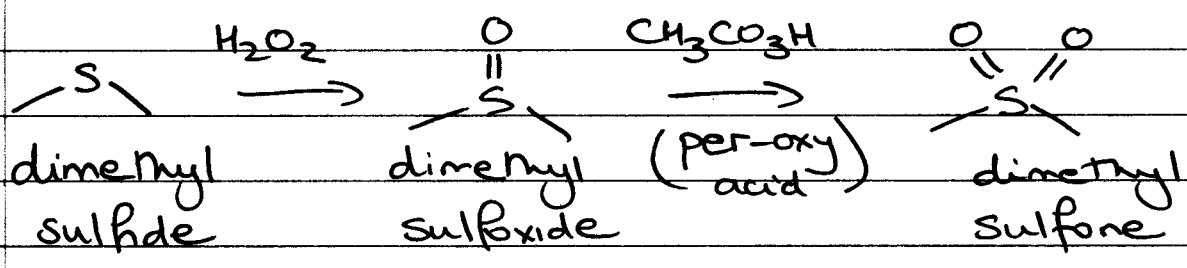
Lower pka → more acidic than R–OH

## (V) OXIDATION

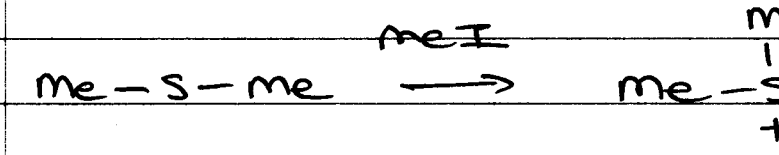
$$R\text{–}SH \xrightarrow{O_2} R\text{–}S\text{–}S\text{–}R$$

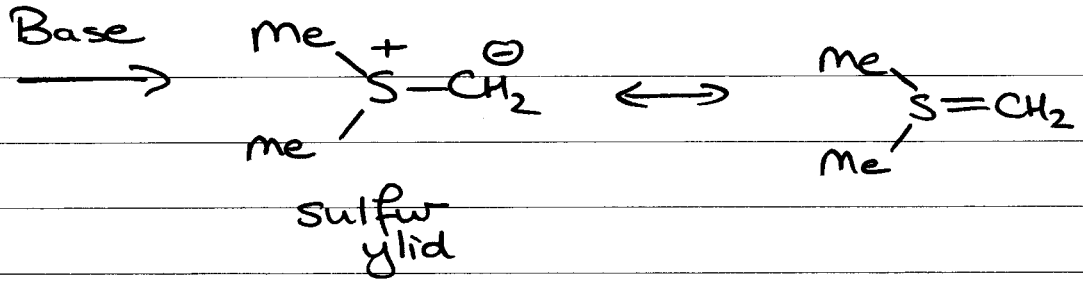
disulfide

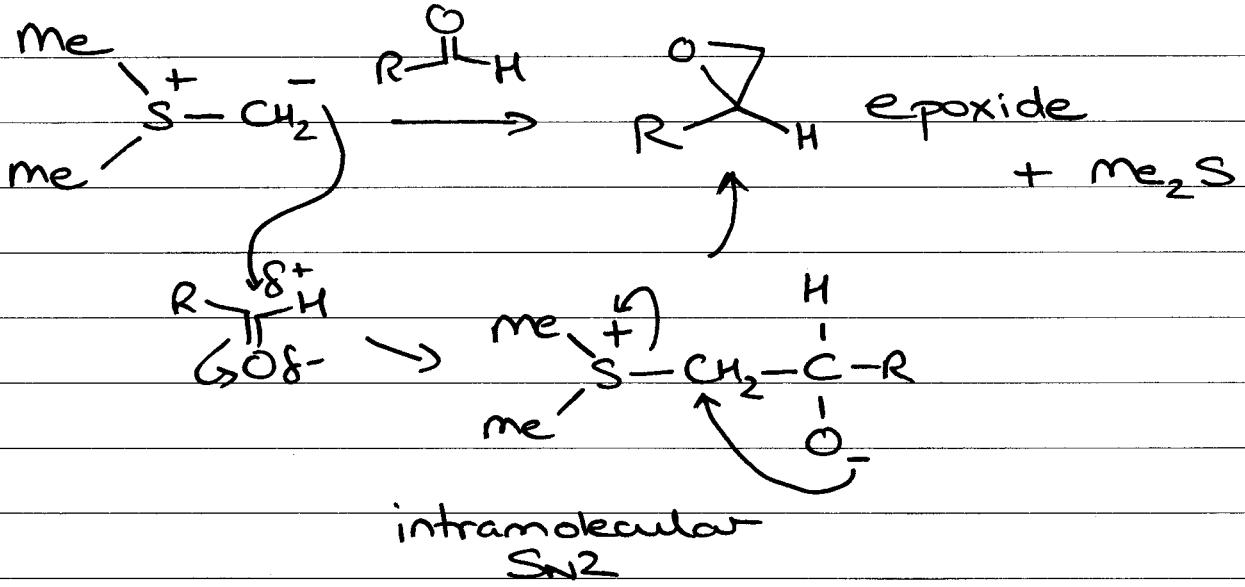
Important in tertiary structure of proteins
DISULFIDE BRIDGES




## (VI) REACTION




Base
me
me
sulfur ylid


epoxide
+ Me2S
intramolecular SN2

LEC (6)

(1) QUIZ 1 AVERAGE = 19/30
$\phi$ - LOW 35 - HIGH

(2) CNSI

(3) HMK 11.2 - 11.9, 11.15 - 11.17

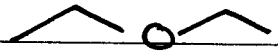
ETHERS

(1) NOMENCLATURE
(2) PHYSICAL PROPERTIES
(3) PREPARATION
(4) REACTIONS
(5) PROTECTING GROUPS

EPOXIDES

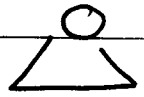
---

(1) R - O - R'



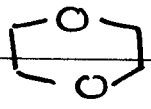
ETHOXYETHANE
DIETHYL ETHER
ETHER

CYCLIC ETHERS



Ethylene oxide

Tetrahydrofuran (THF)



1,4 Dioxane

SPECIAL ⇒

(2) $\overset{\delta+}{CH_3}-\overset{\delta-}{O}-\overset{\delta+}{CH_3}$ weakly polar bp -24°C

$CH_3CH_2OH$ strongly polar bp 78°C

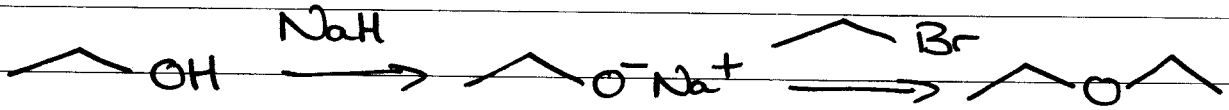
- Quite stable
- Generally quite inert in relative terms

$\Rightarrow$ GOOD SOLVENTS

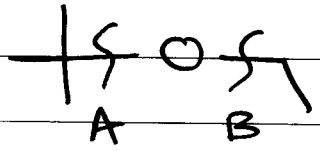
## (3) PREPARATION

### (i) WILLIAMSON ETHER SYNTHESIS

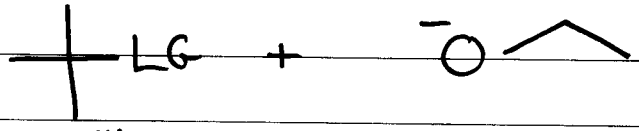
$$R-OH + R'-LG \xrightarrow{\text{Base}} R-O-R'$$

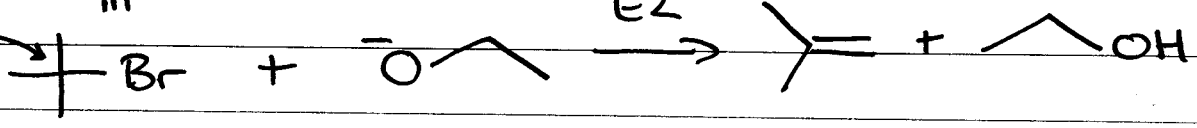



Consider

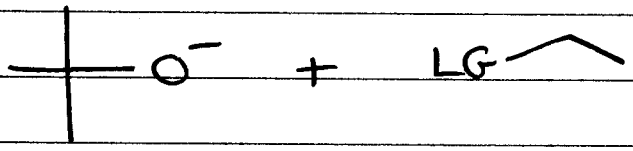


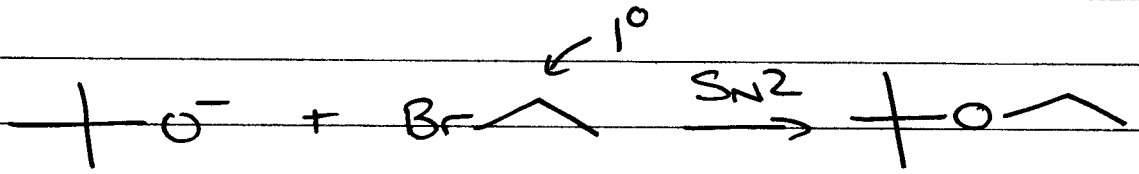

DISCONNECTIONS

(A) 

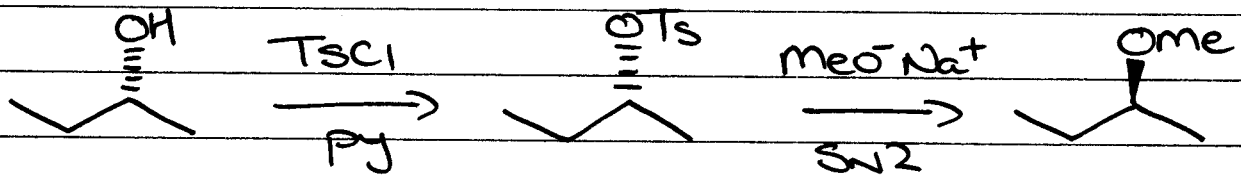

3° 

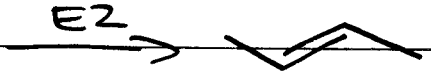
(B)





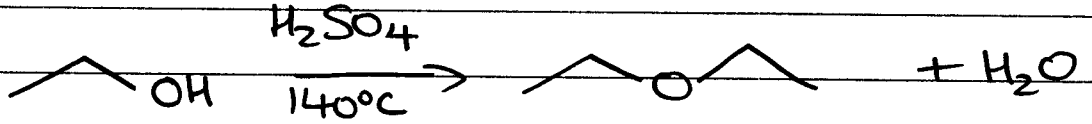

ETHERS FROM 2° ROH



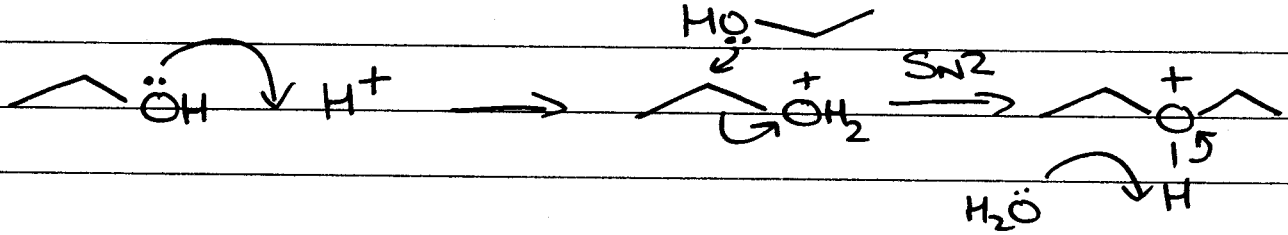




MIXTURE

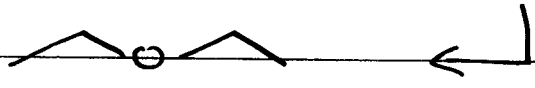
(ii) ACID CATALYZED DEHYDRATION of R-OH




Good for SYMMETRICAL ethers
UNBRANCHED




TEMP control
for ETHER vs ALKENE

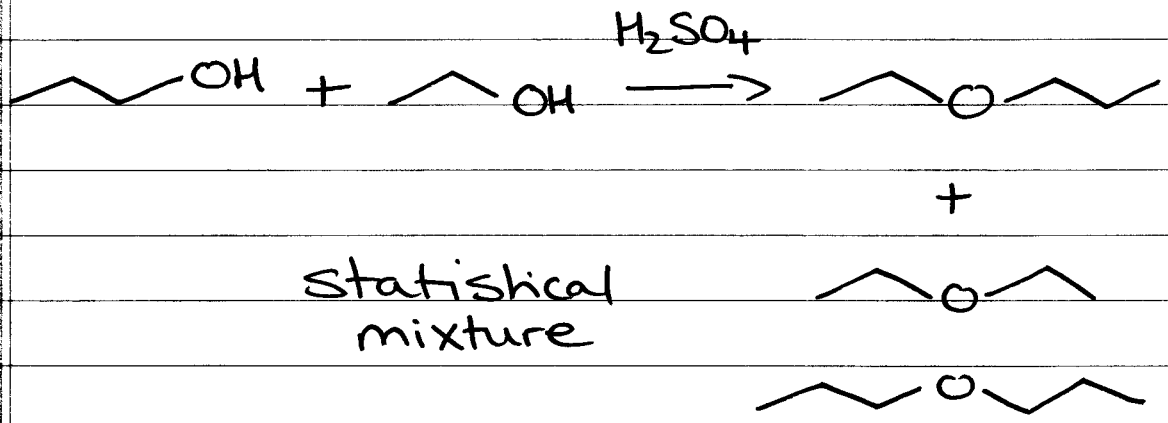


2° R–OH ⟶ product mixture

ETHERS from SUBSTITUTION
ALKENES from ELIMINATION

3° R–OH ⟶ alkenes from ELIMINATION

– ONLY GOOD FOR 1° R–OH

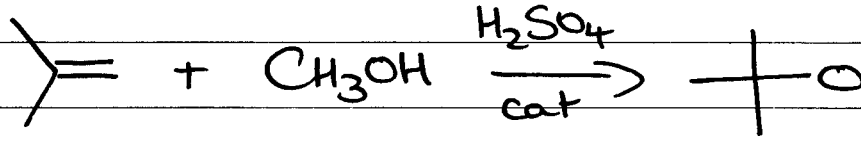


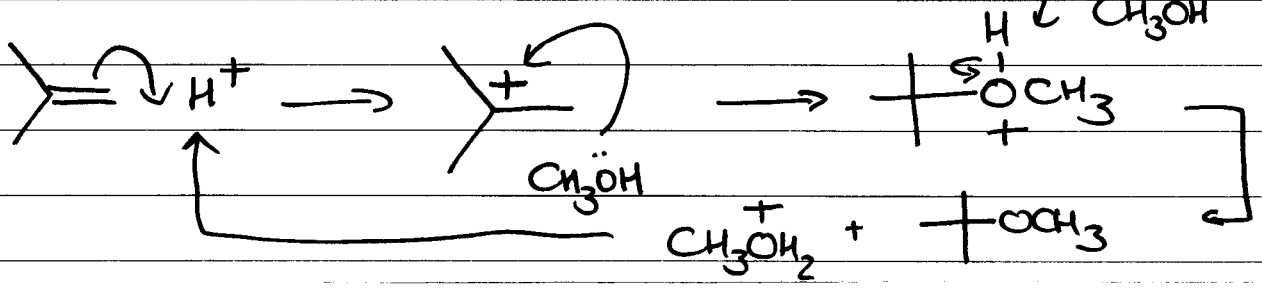

statistical mixture

(iii) ALKENE + ALCOHOL $\xrightarrow[\text{cat}]{\text{Acid}}$ ETHER

↑ be able to form stable C+

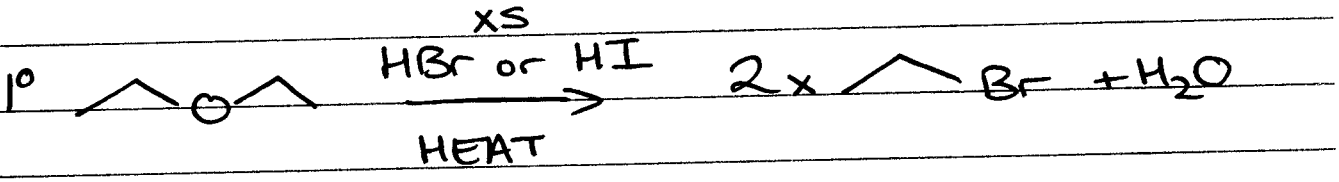
↑ not be able to dehydrate



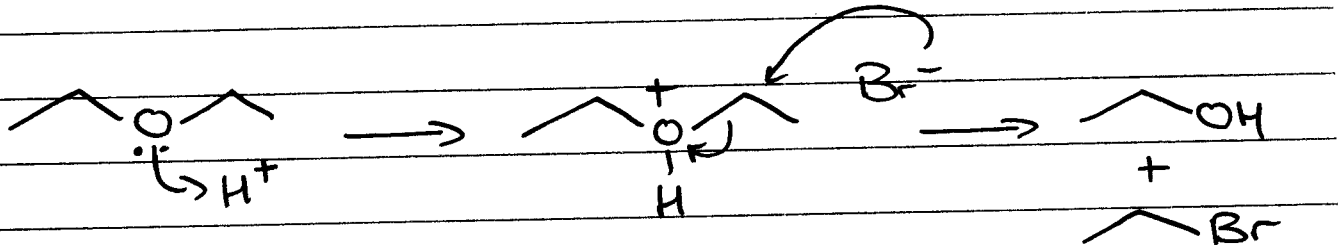



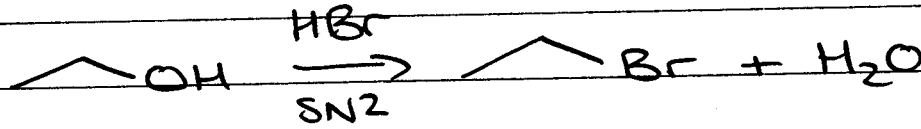
## (4) REACTIONS OF ETHERS

### (1) ACID CATALYZED CLEAVAGE

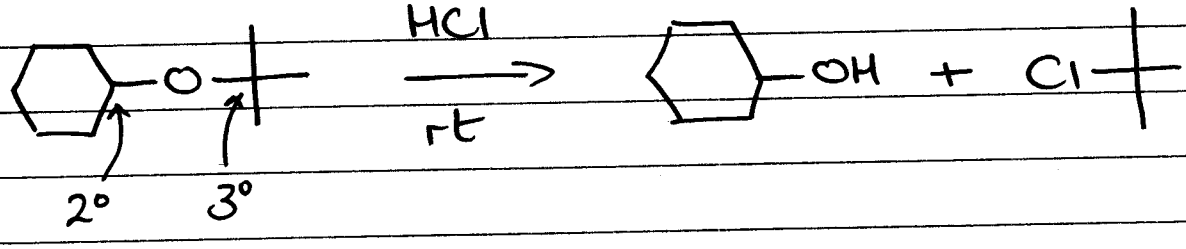


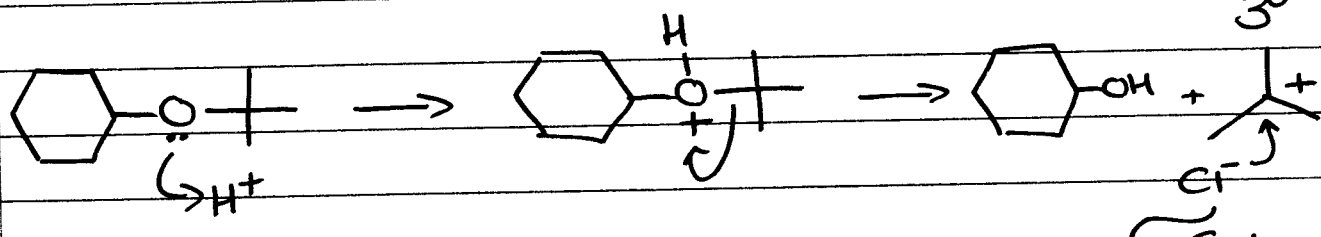

(not HCl, $Cl^-$ not nucleophilic enough)

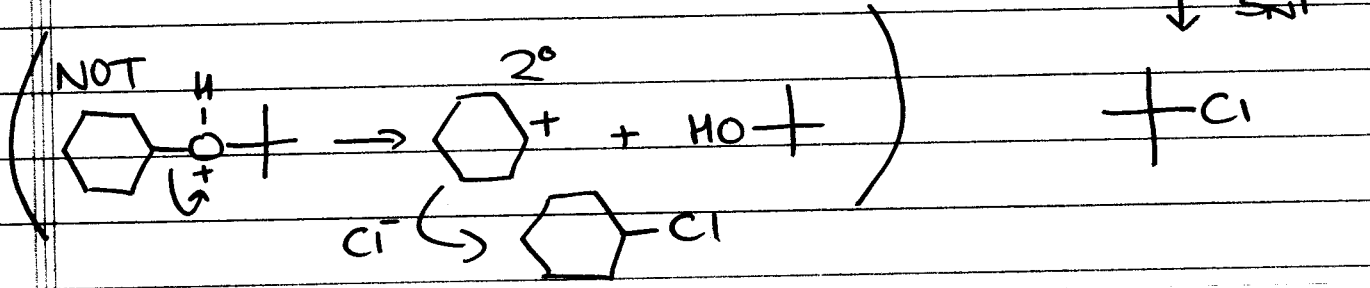


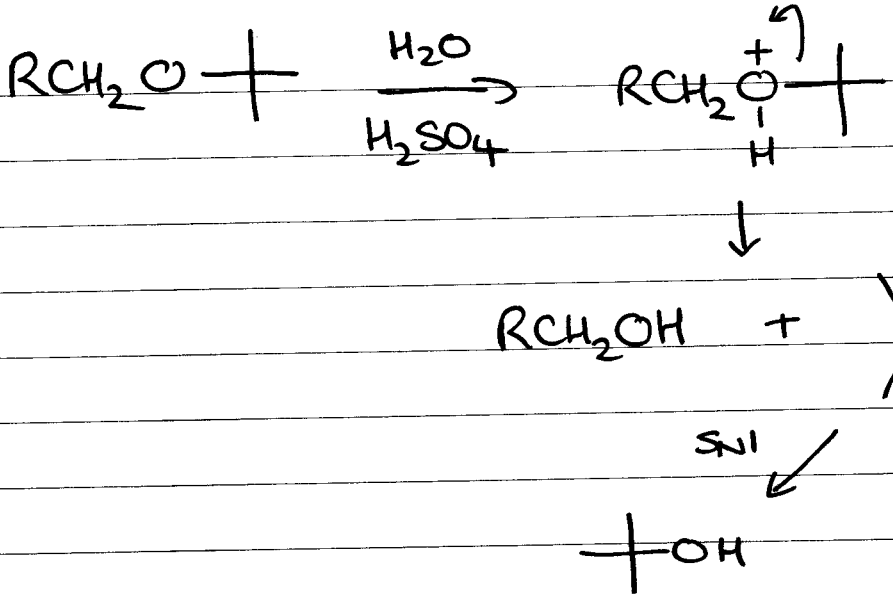




2°/3°

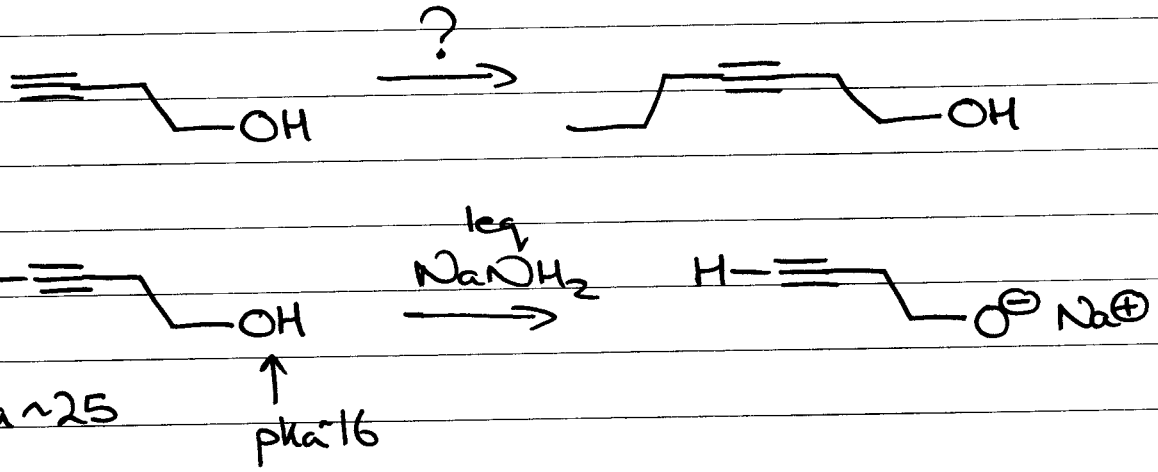


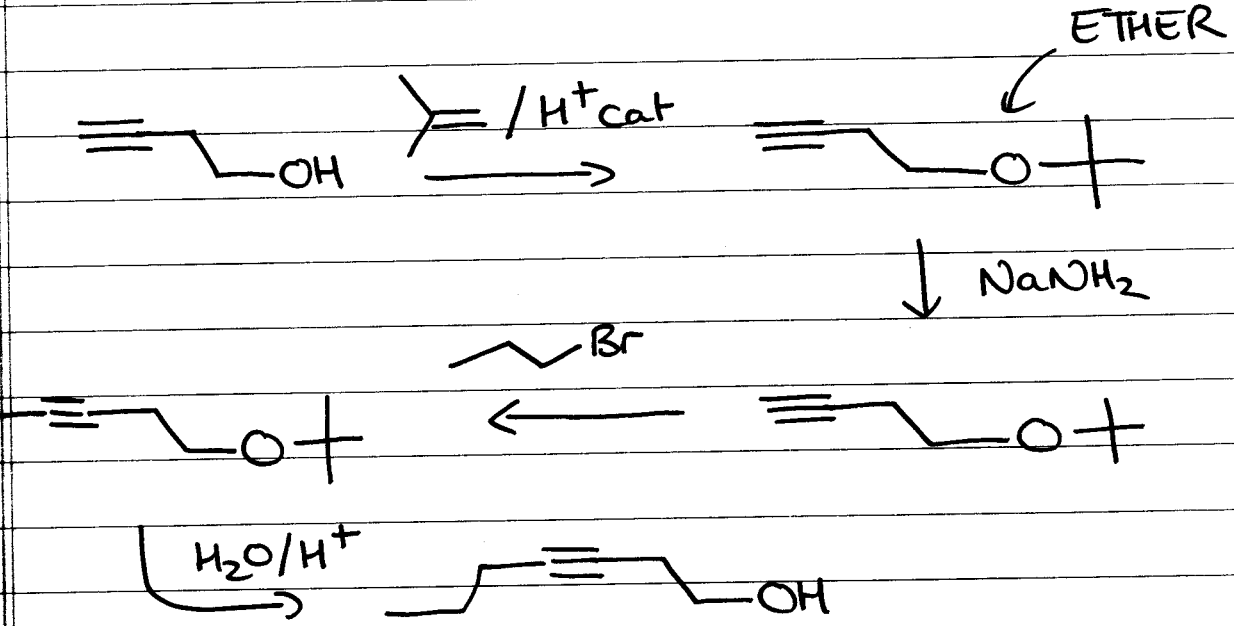





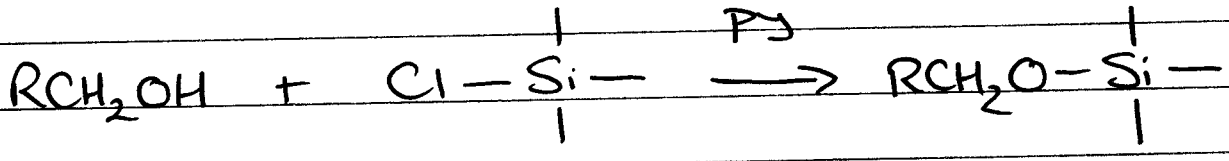

## (5) PROTECTING GROUPS

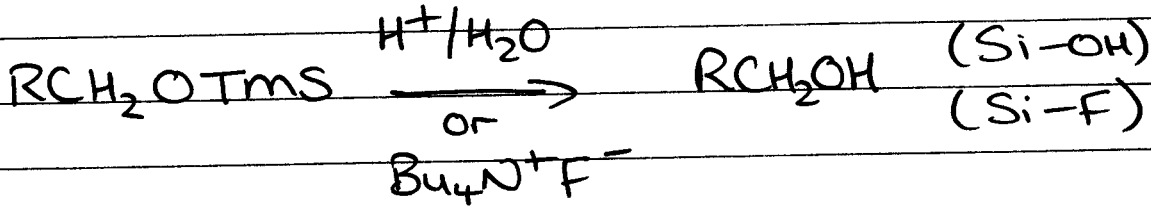


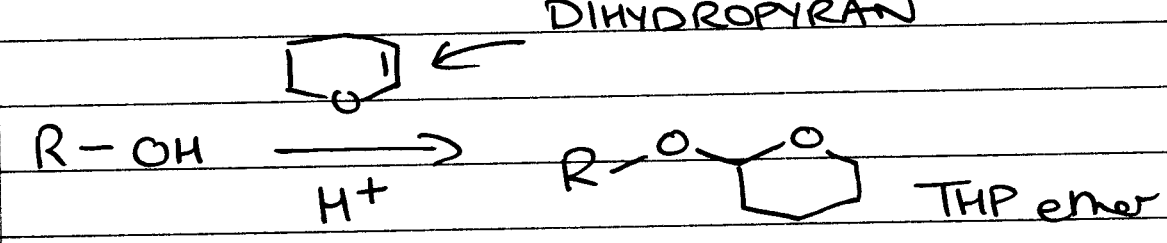
# Other protecting groups.

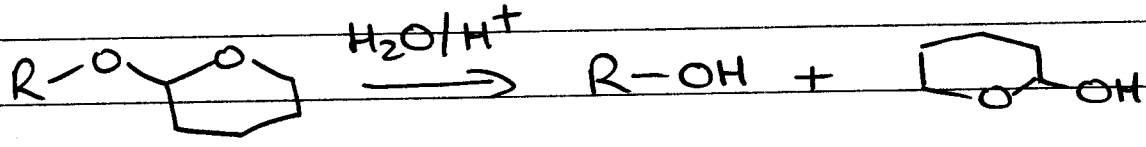
## (i) SILYL ETHERS



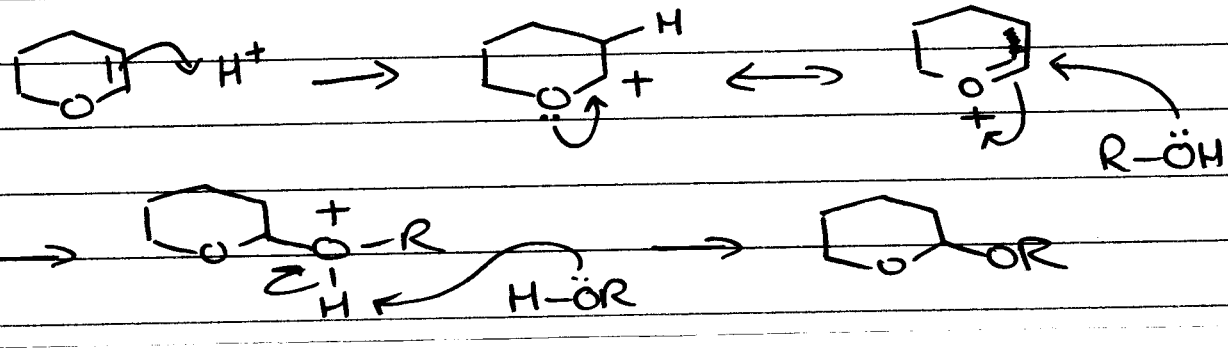




## (ii) THP ethers

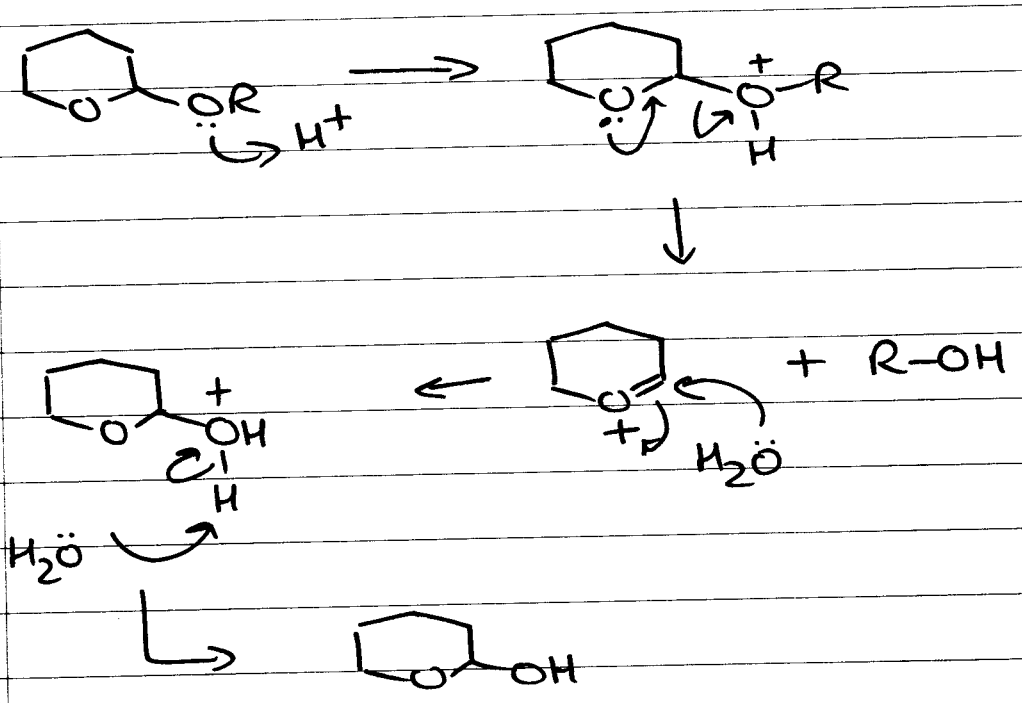


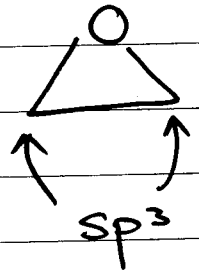

MECHANISM:



# Deprotection



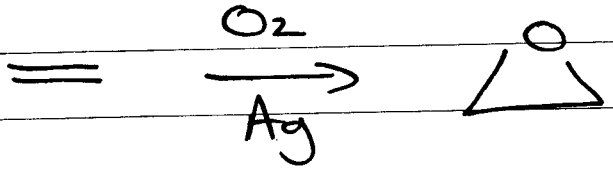

# EPOXIDES




HIGHLY strained

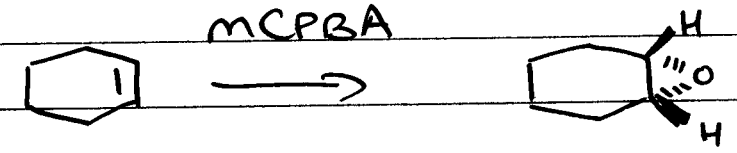
↳ distorted bond angles

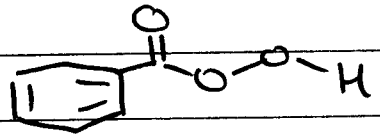
## (i) INDUSTRIAL SYNTHESIS




doesn't work for other alkenes

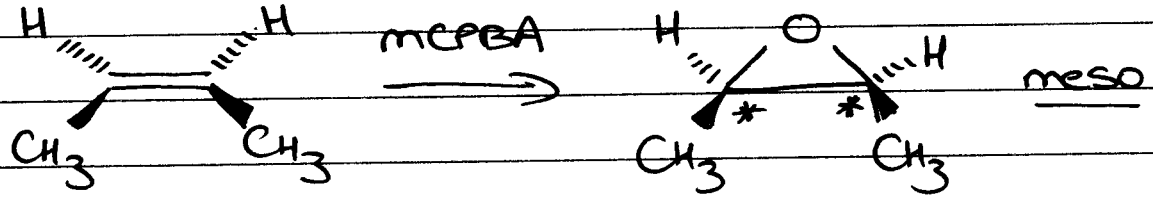
## (ii) using peroxyacids

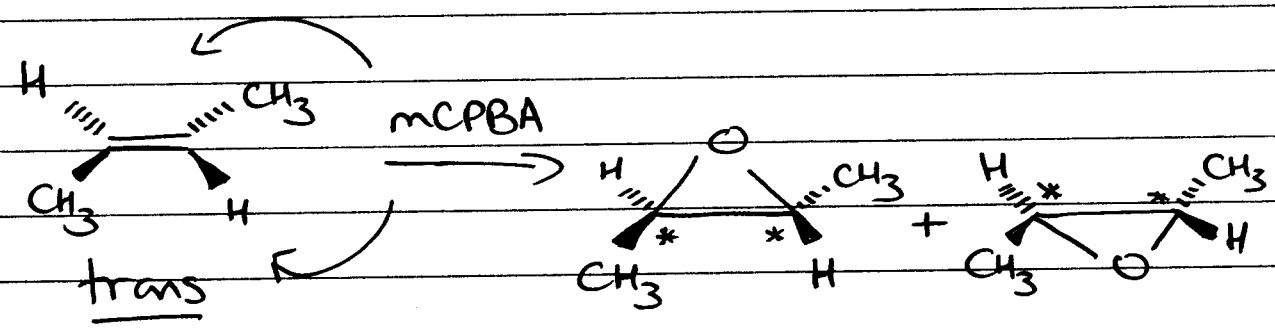


metachloroperoxybenzoic acid.

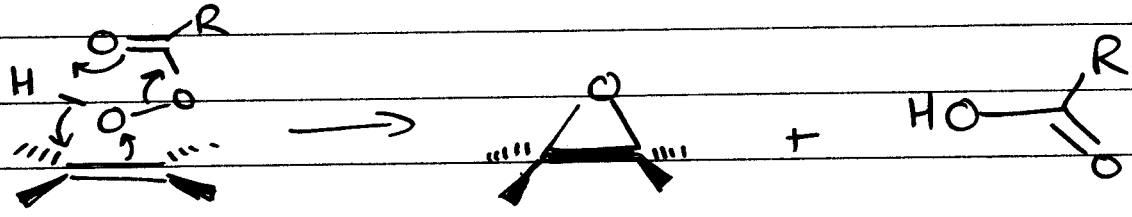
STEREOSPECIFIC




ENANTIOMERS

mechanism

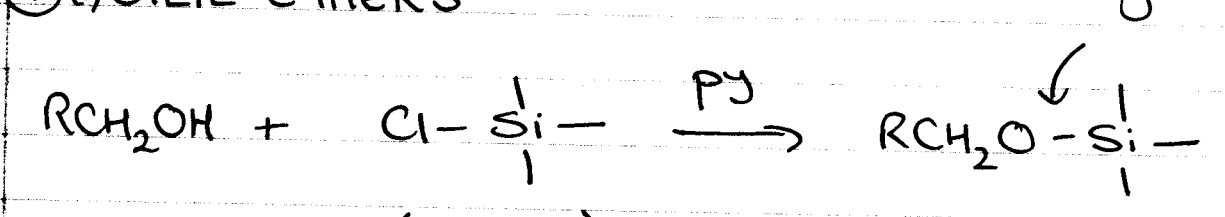


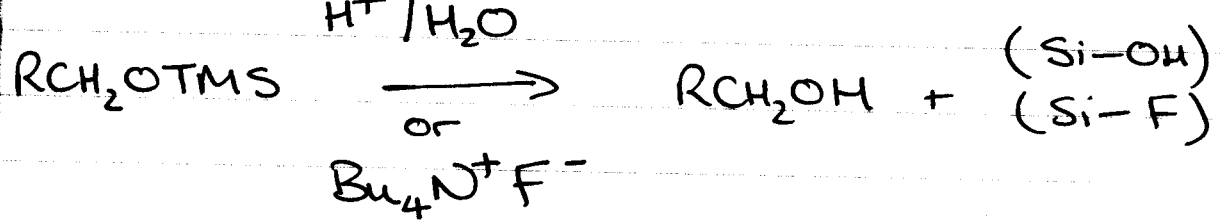
Lec (7) 

(1) CNSI Lecture
Tues 5pm CS50
(2) HMK 11.19 – 11.40
Tim Swager MIT "Polyptycenes: Nanostructures for Electronic, Photonic, and Structural Materials"

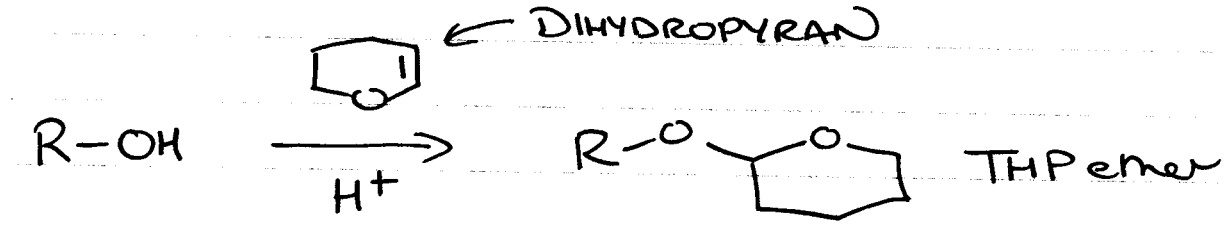
(1) ETHER PROTECTING GROUPS
(2) EPOXIDES
  (i) SYNTHESIS
  (ii) REACTIONS
  (iii) THIOETHERS

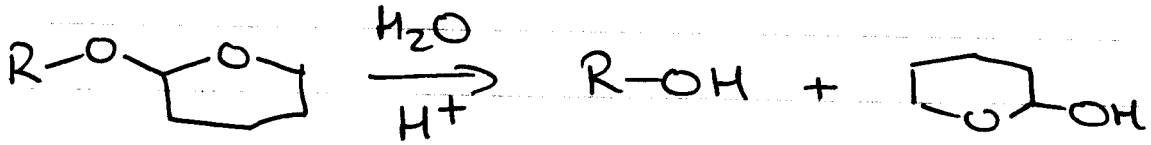
(1)(i) SILYL ETHERS



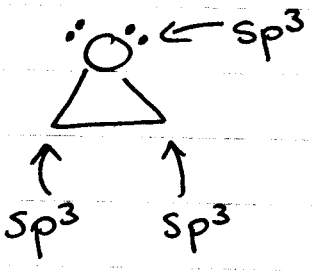
(ii) THP ethers (2)



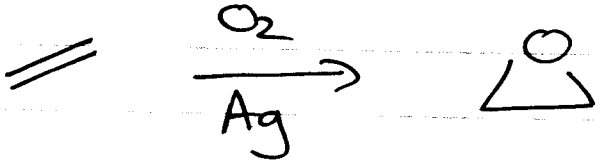

Work out mechanism for both of these reactions.

(2) EPOXIDES



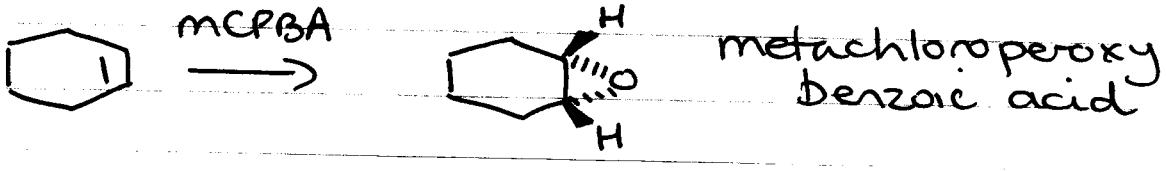

HIGHLY STRAINED
↳ very distorted bond angles

(i) INDUSTRIAL SYNTHESIS

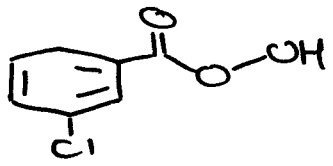



doesn't work for other alkenes

LAB SYNTHESIS → PEROXYACIDS

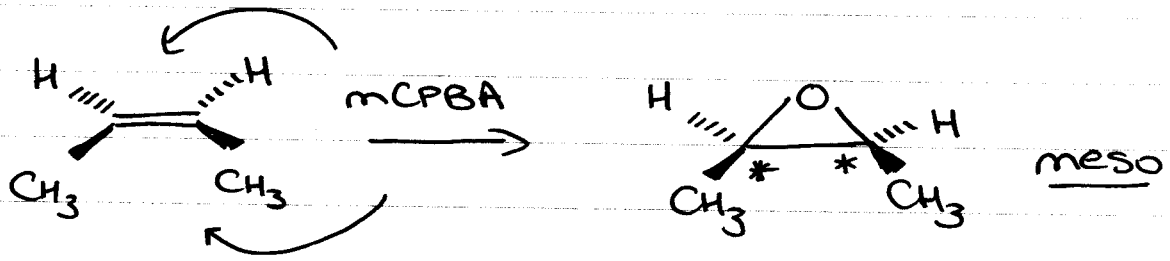



metachloroperoxy benzoic acid

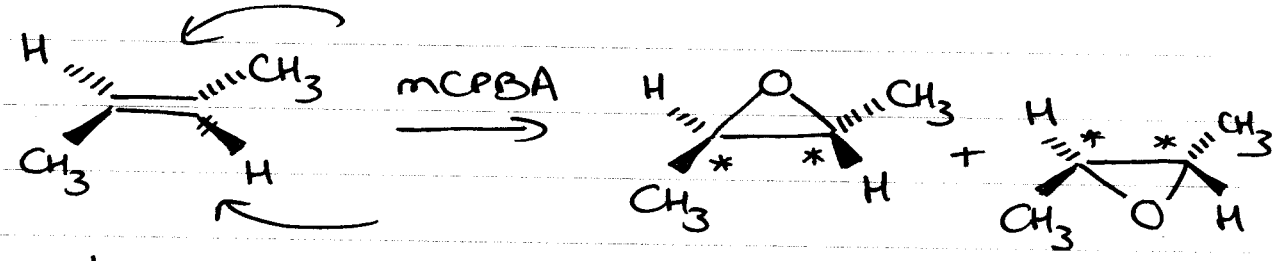
mCPBA = 

STEREOSPECIFIC





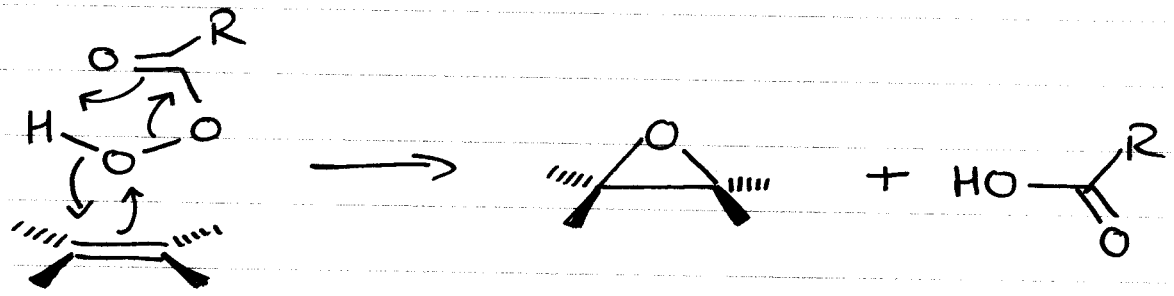

cis




trans

ENANTIOMERS

mechanism:



SHARPLESS ASYMMETRIC EPOXIDATION

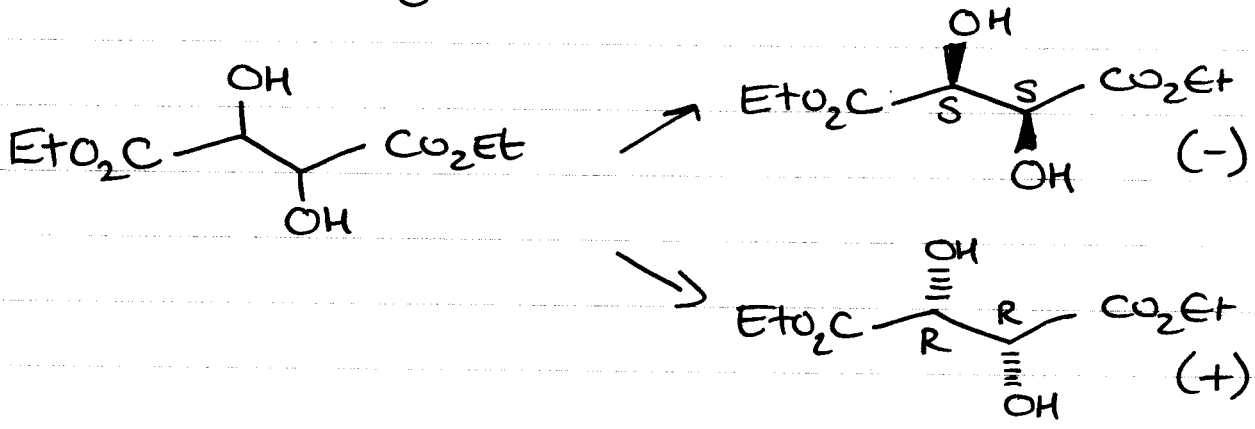
↑ NOBEL PRIZE IN CHEMISTRY 2001

Epoxidation of allylic alcohols

$t$-BuOOH / $Ti(O^iPr)_4$ / DET (+/−)

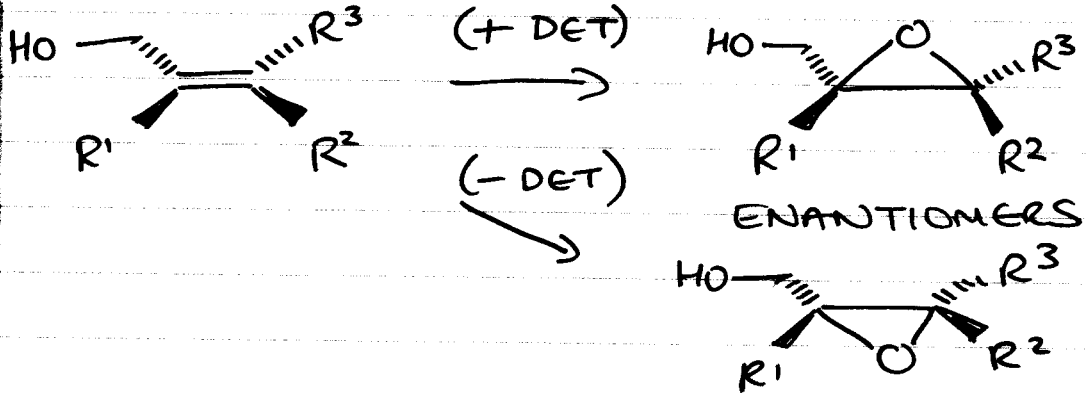
$t$-butyl peroxide

DET = Diethyltartrate

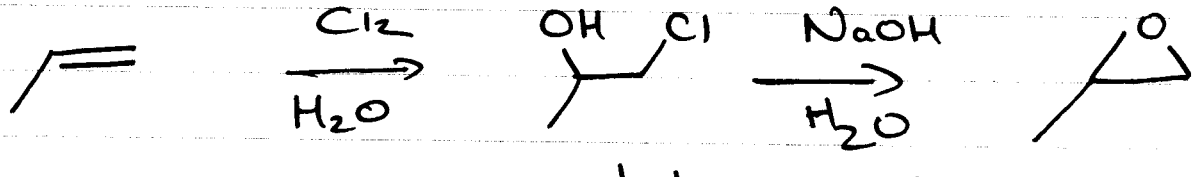



Peroxide / Ti / DET / Allene ⇒ complex

↑ selectivity.

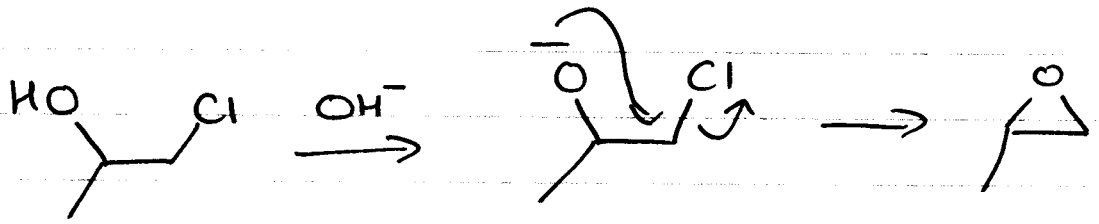



VIA HALOHYDRINS



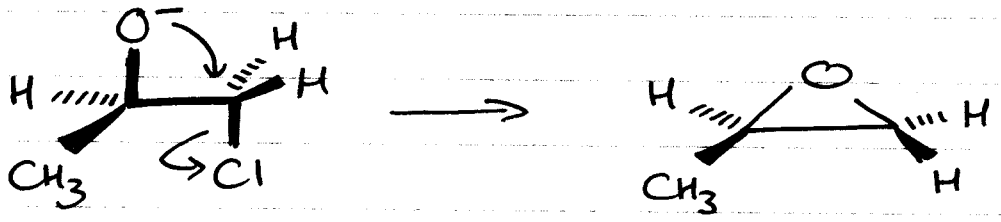

Intramolecular $S_N2$

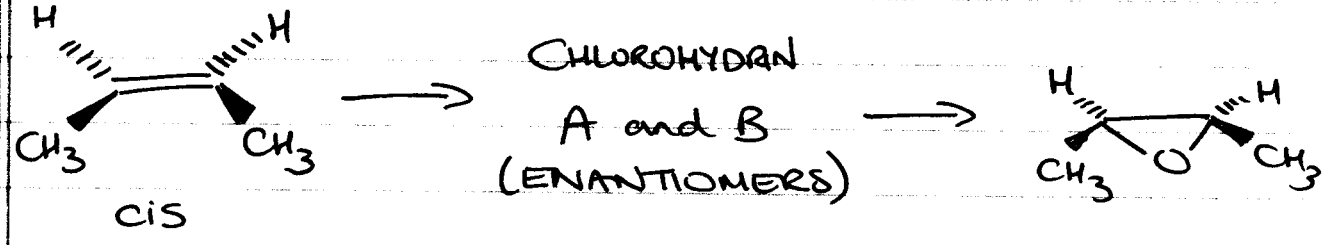
Mechanism



chlorohydrin

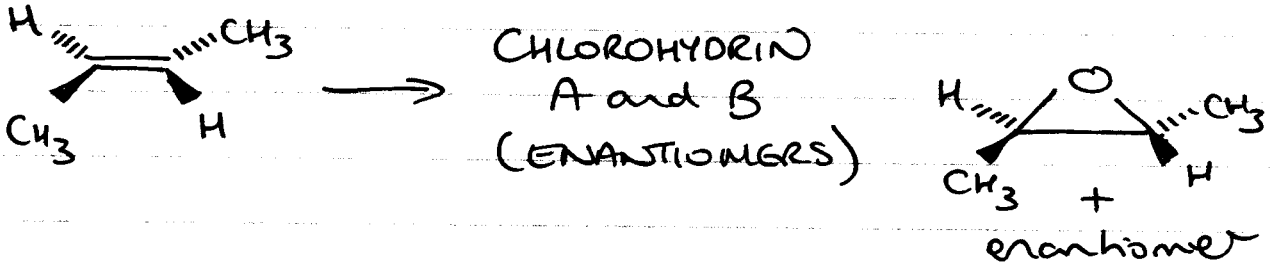
STEREOSPECIFIC






cis

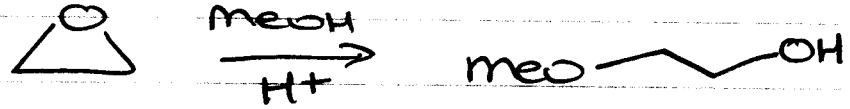
meso



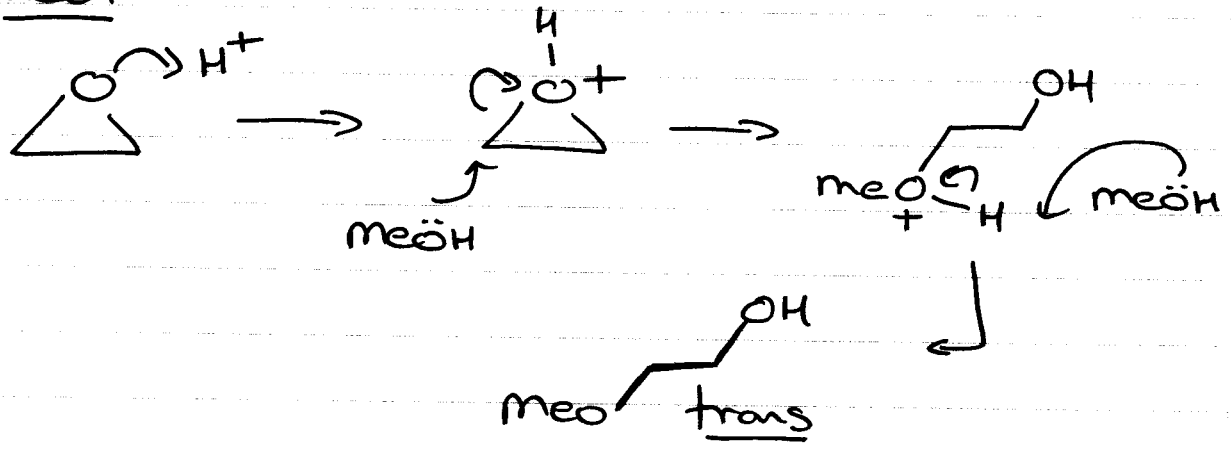

+ enantiomer

(ii) REACTIONS

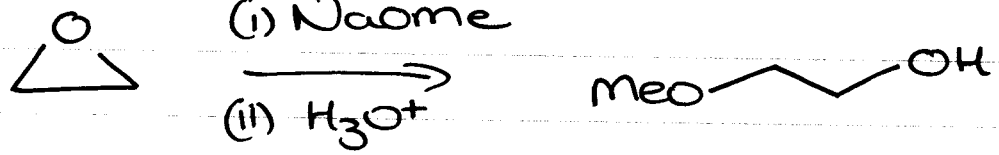
ACID CATALYZED RING OPENING

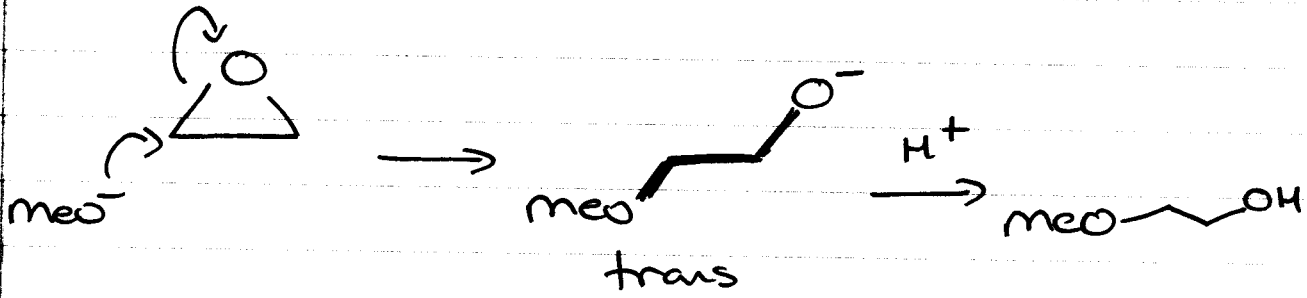


mech:

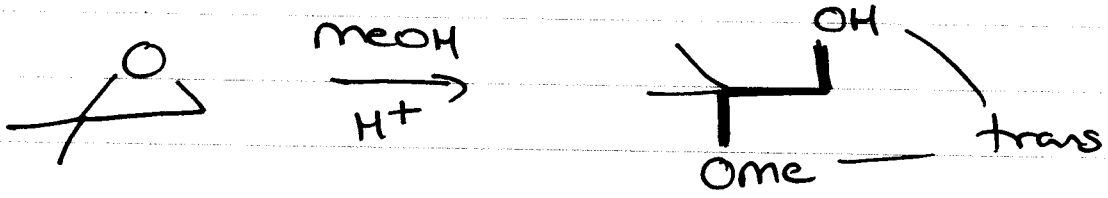


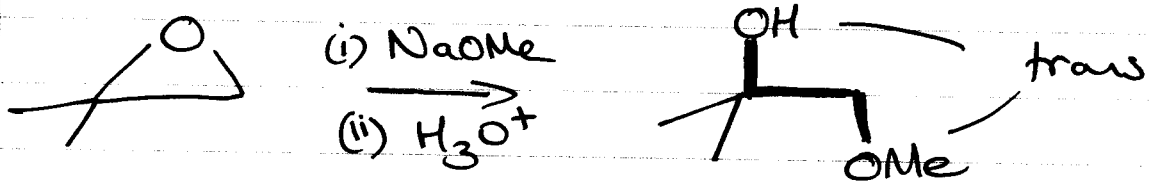

## NUCLEOPHILIC RING OPENING



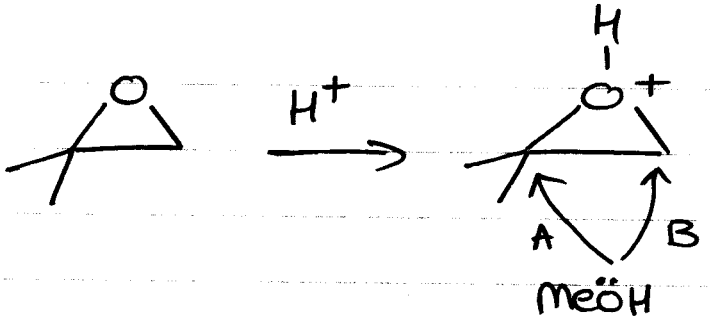

Consider



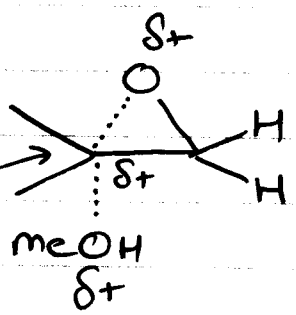

WHY ?

Acid



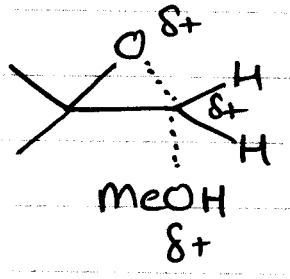

Concerted rxn, but build up of +ve in TS on C that is attacked.

(A)




Opens via more stable C+

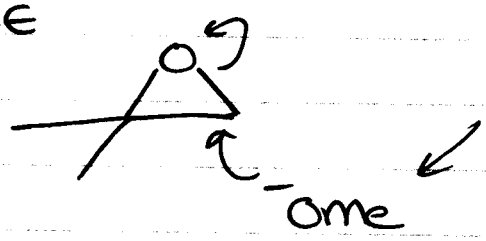
(B)



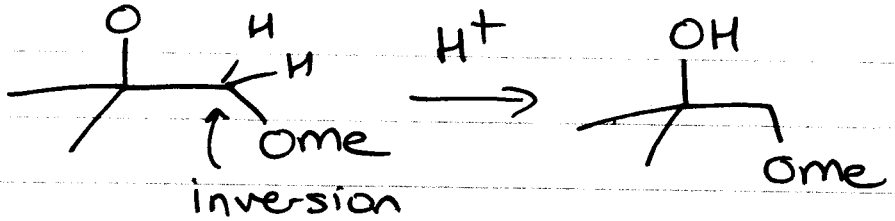

also get inversion → $S_N2$

OMe ends up on more substituted C atom

BASE

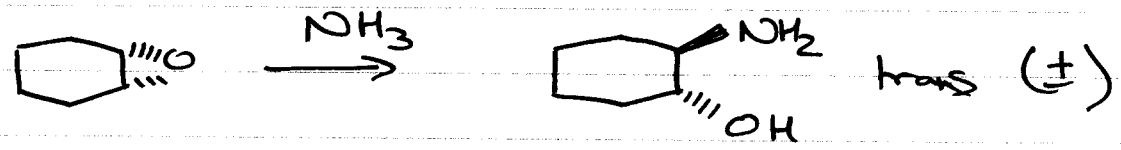


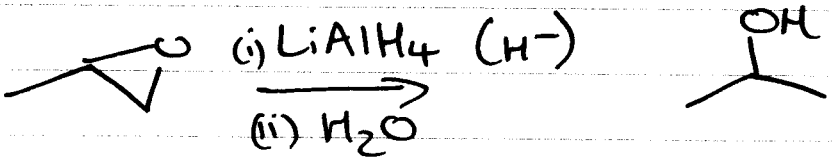

Nucleophile ~~hinders~~ attacks least hindered carbon



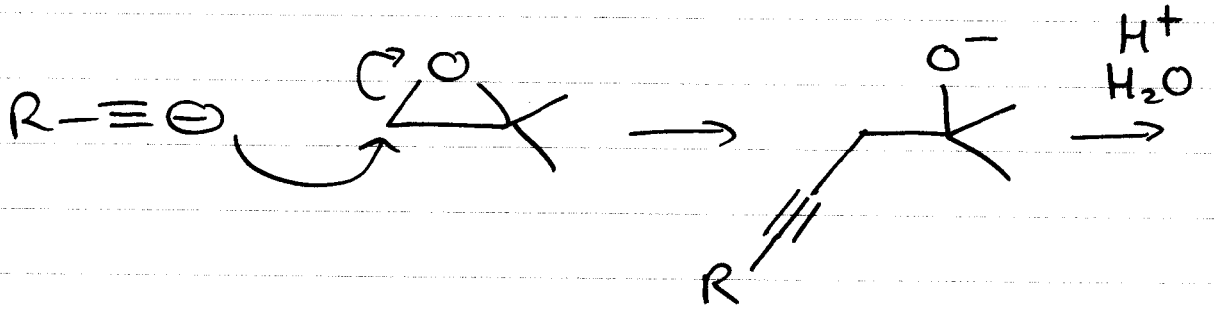

OMe ends up on least sub C atom

Open epoxides w/ other nucleophiles


also acetylide nucleophiles

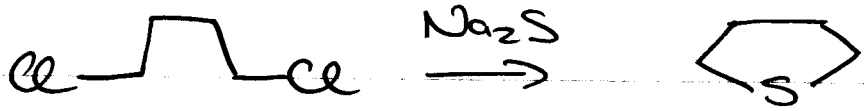




(iii) THIOETHERS

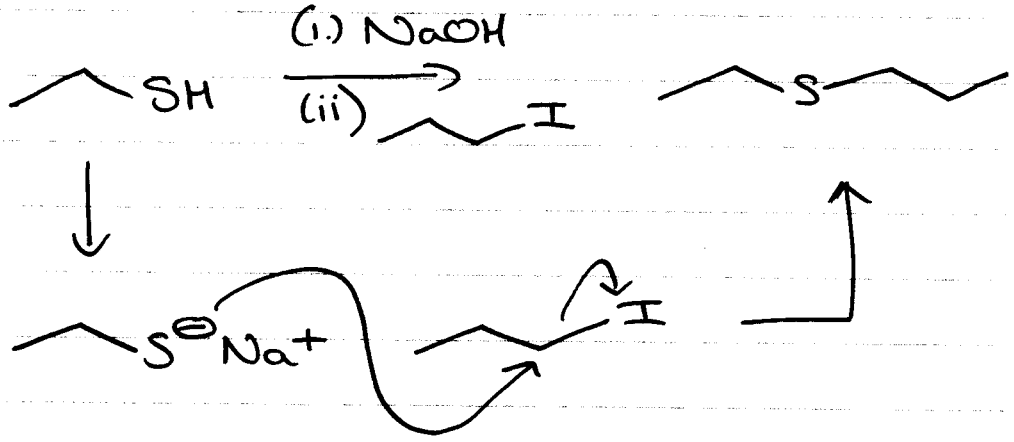
Symmetrical sulfides

$2RX + Na_2S \longrightarrow R-S-R + 2NaX$

$S^{2-}$ is the nucleophile




Unsymmetrical (WILLIAMSON)




Don't worry about crown ethers

LEC 8



1. OUTREACH PROGRAM 7-9 pm
2. HMK

15.1 – 15.4, 15.7, 15.9 – 15.15, 15.17, 15.24 – 15.26

---

1. REACTIONS OF EPOXIDES
2. THIOETHERS
3. ORGANOMETALLICS OVERVIEW
   - (i) OVERVIEW
   - (ii) MAGNESIUM
   - (iii) LITHIUM
   - (iv) COPPER
   - (v) ~~RUTENT~~ RUTHENIUM

---

1. EPOXIDES ... consider.
2. THIOETHERS

3. Chapter 15 → NO HECK

Compounds M–C bond ($\delta+$ $\delta-$) (EXTREME RESONANCE $M^+C^-$)

POLAR COVALENT BOND (not salts)

V. important in synthesis
esp C–C BOND formation

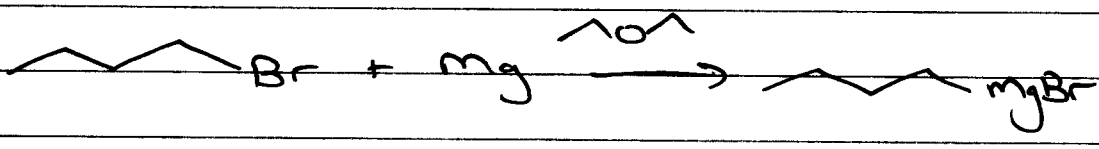
generally very reactive, often moisture sensitive

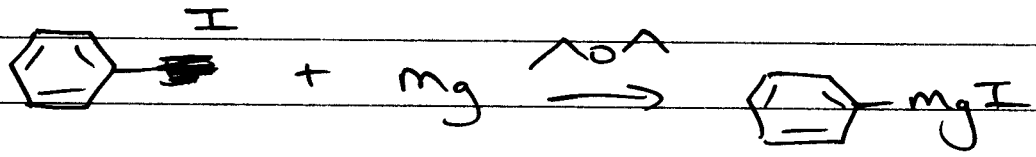
(i) ORGANOMAGNESIUM compounds
(GRIGNARD Reagents)

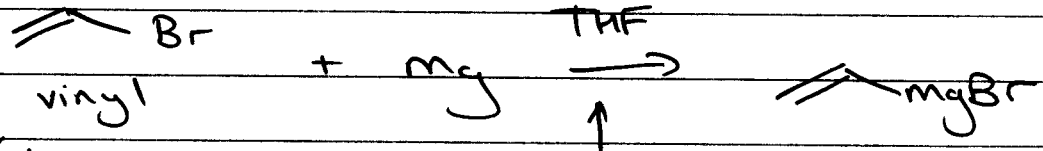
"R – Mg – X" ⟸ write like this, but actual structure is debatable (solvated / clusters)

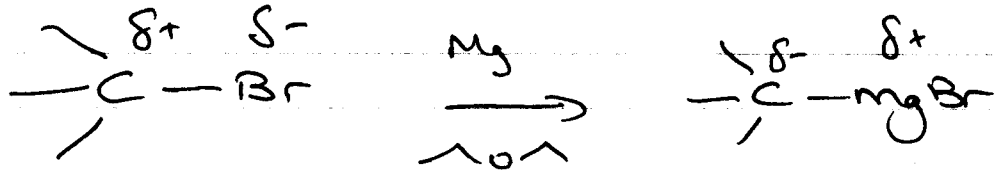
↑ alkyl/aryl ↑ halogen

Preparation: add halide to Mg in ether



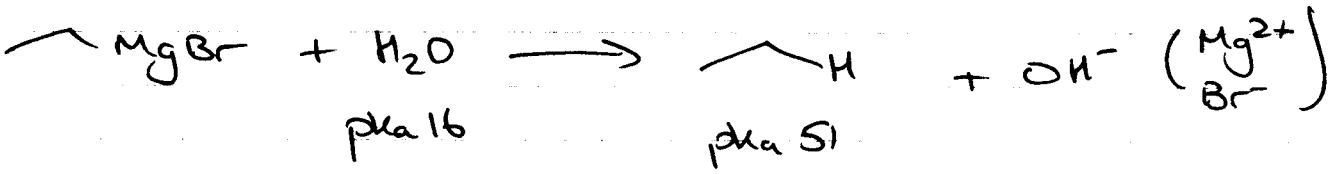






Electrophilic C atom

Nucleophilic C atom ($R^-$)

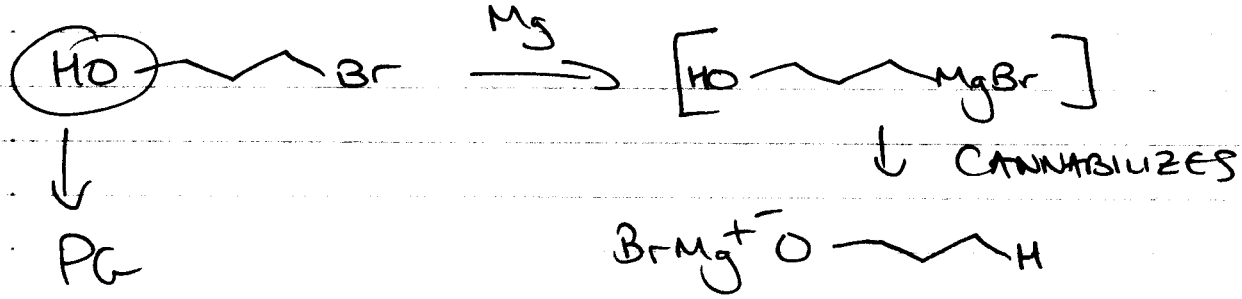
Reactions:



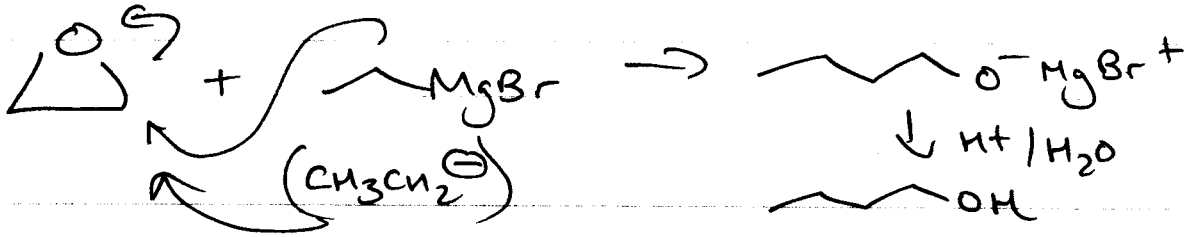

v. strong base — will deprotonate

| | $RNH_3$ | $RC\equiv CH$ | ROH | RSH | RCOOH |
|---|---|---|---|---|---|
| pka | ~38 | 25 | 16 | 9 | 5 |

50/




RXN w/ EPOXIDES



LEC (9)

(1) MIDTERM next WEDS → To end of todays lecture
(2) HMK 15.1–15.4, 15.7, 15.9–15.15, 15.17, 15.24–15.26
(3) APRIL 23rd !!

---

(1) COPPER → GILMAN
                → SIMMONS–SMITH
(2) RUTHENIUM

---

(1) RECAP...

$R\text{-}MgX$ / $R\text{-}Li$ $\xrightarrow{R'\text{-}X}$ $R\text{-}R'$ not good rxn

COPPER (i) GILMAN REAGENTS

$$2\ R\text{-}Li + CuI \xrightarrow[(THF)]{ether} R\text{-}\underset{Li^+}{\overset{\ominus}{Cu}}\text{-}R + LiI$$

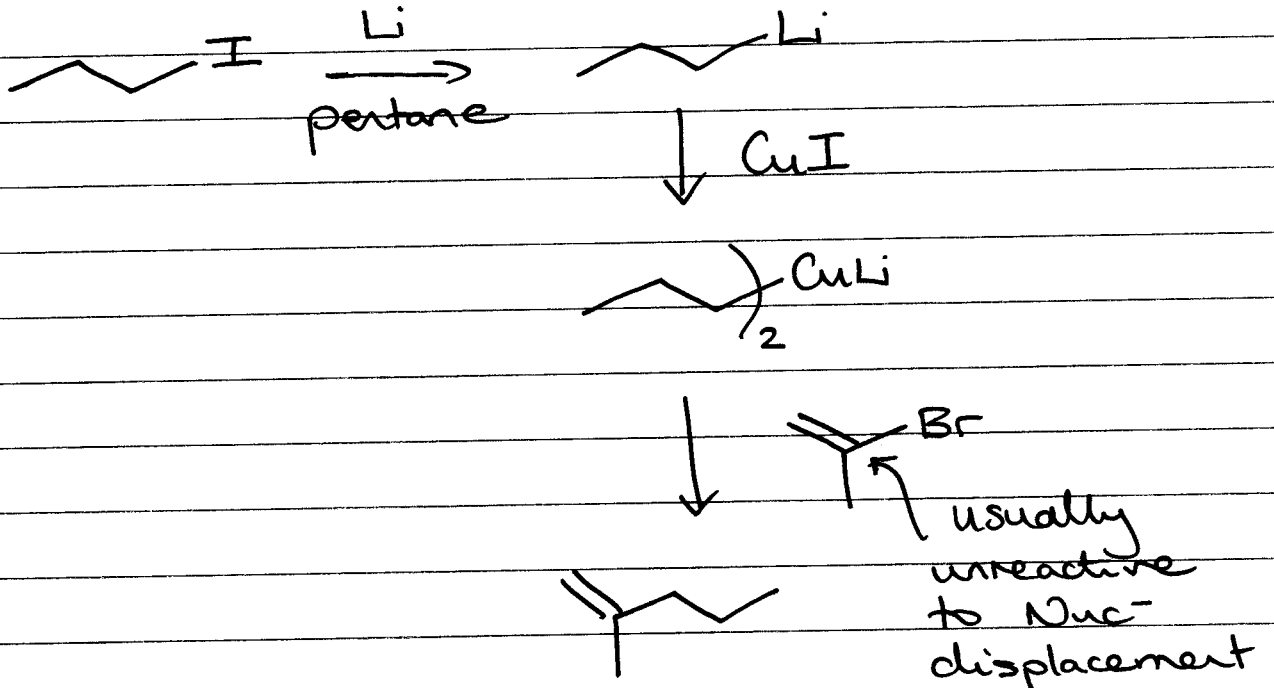
$$\text{(cyclohexyl)}_2CuLi \xrightarrow[ether]{R\text{-}Hal} \text{(cyclohexyl)-}R$$

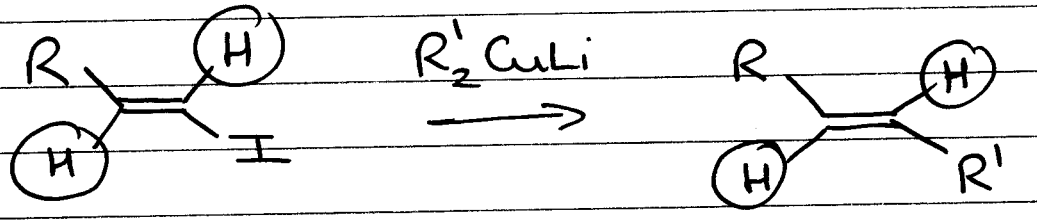
R–Hal =  , $RCH_2Br$,  , 

vinylic  1° alkyl  allylic  aryl

also reacts w/ 

(see again in C=O chemistry)



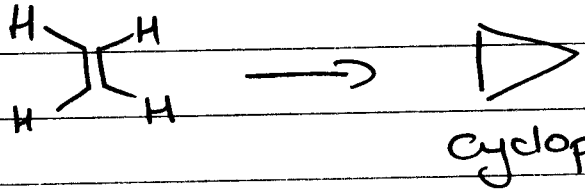




configuration retained

## (ii) SIMMONS-SMITH RXN

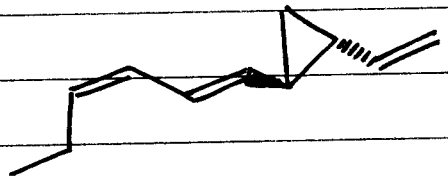
$$CH_2I_2 + Zn/Cu \xrightarrow{\text{ether}} ICH_2ZnI$$

↑ Small amount



cyclopropane

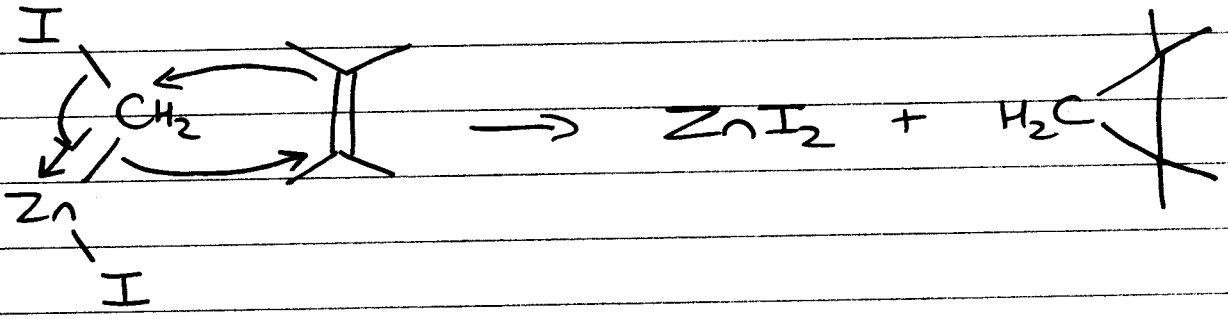
"Source of" $CH_2$



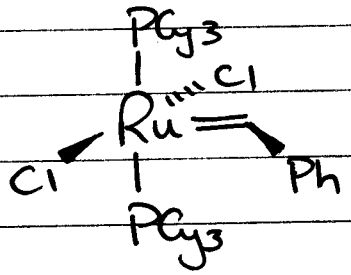
DICTYOPTERENE

'Smell of the sea'

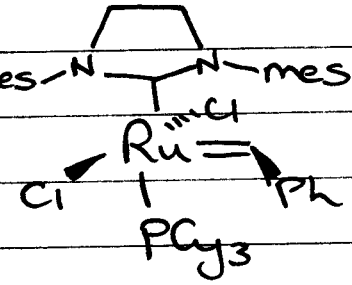
Mechanism



## (2) RUTHENIUM

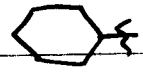


or



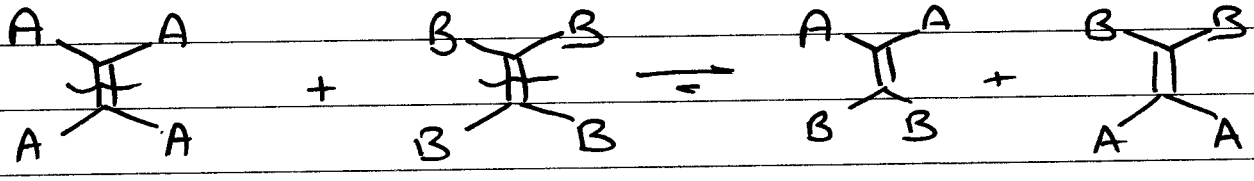
Mes =

Cy =



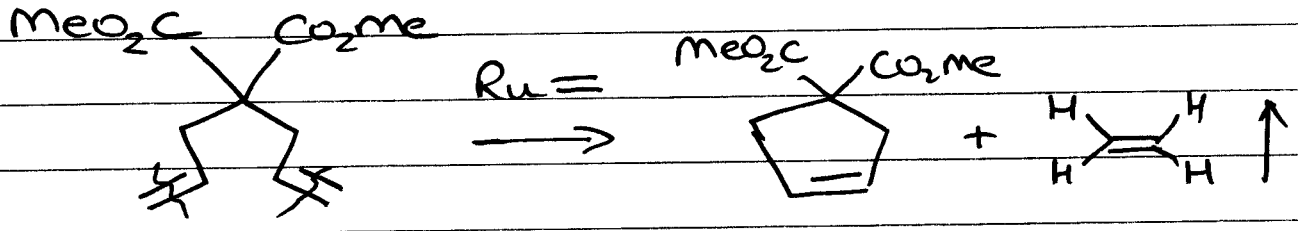
Ru= ← abbreviated

Alkene metathesis



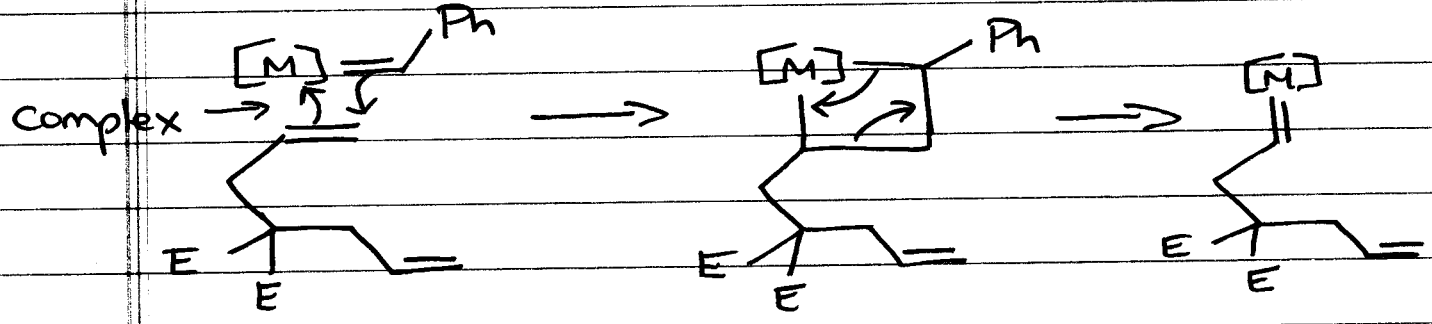

Interchange of C atoms of C=C bonds

RING CLOSING METATHESIS




DRIVING FORCE

Mechanism

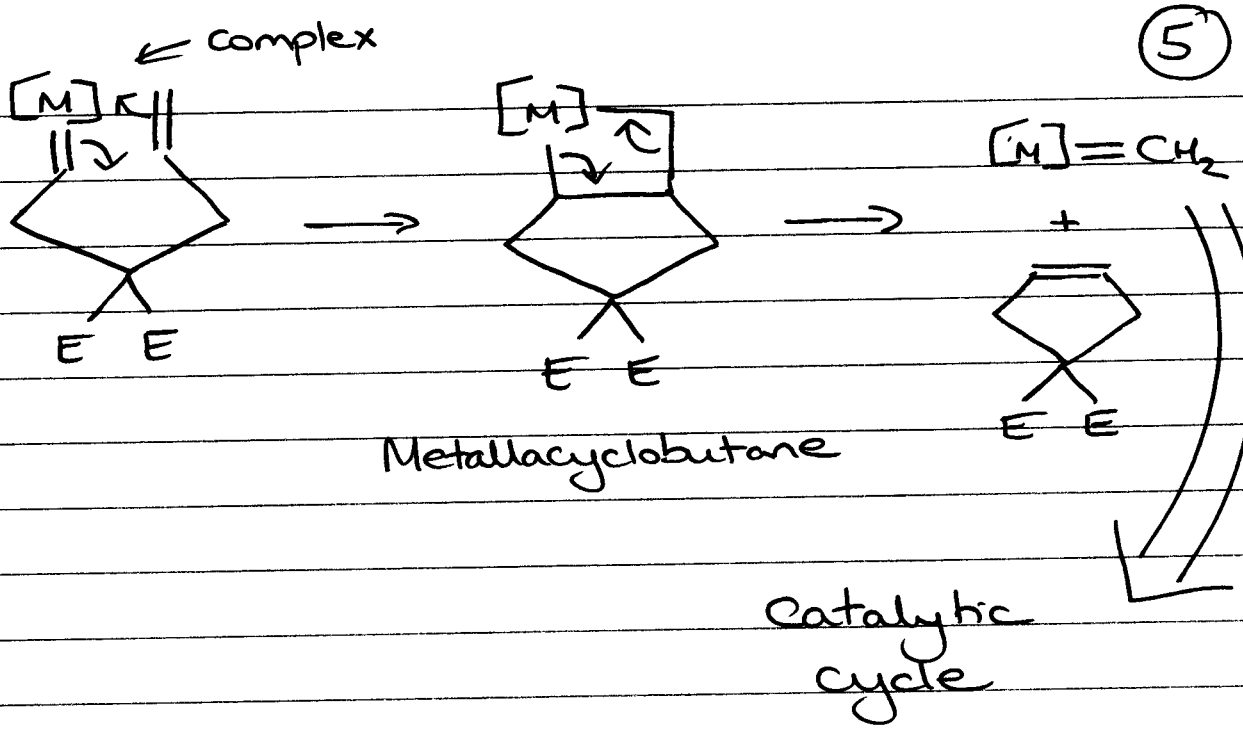


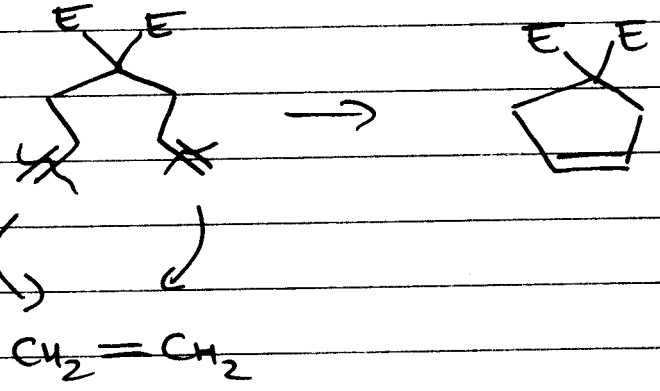

METALLACYCLO-BUTANE

+

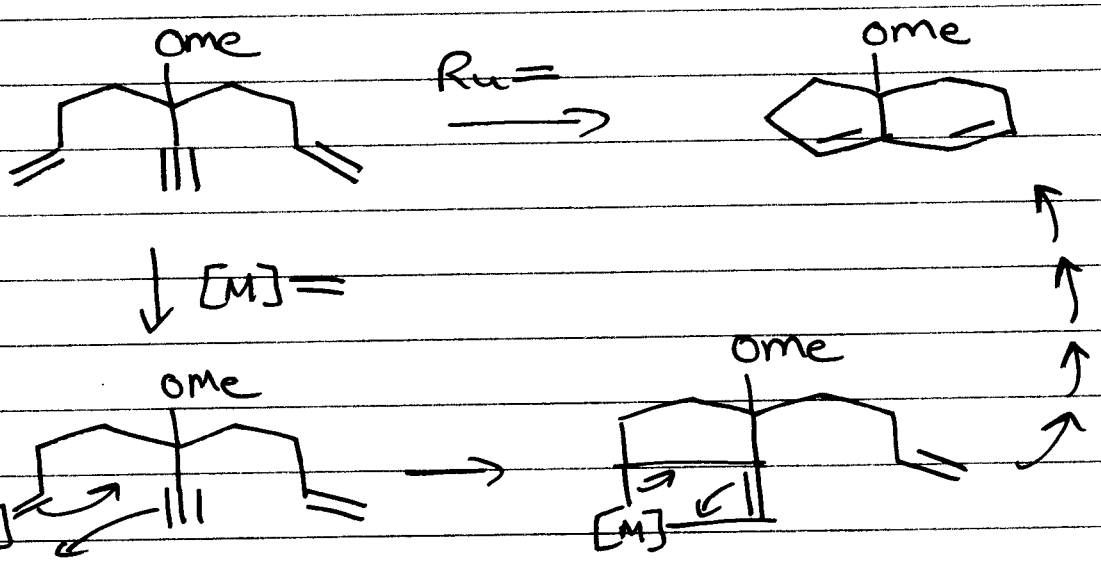



(switched C=C ends




## ALKYNE RELAY



# LEC (10)

1. MIDTERM WEDNESDAY
   ↳ BOOKS
2. CNSI Lecture
   Bruce Dunn — UCLA
   "Assembling Nanodimensional Materials into Energy Storage Systems"

---

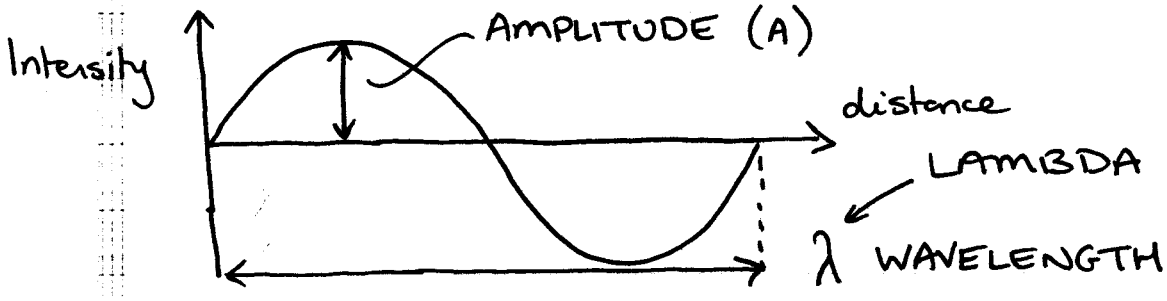
## (1) INTRO to SPECTROSCOPY

Molecular spectroscopy →
study of the interaction between
MATTER & ELECTROMAGNETIC RADIATION

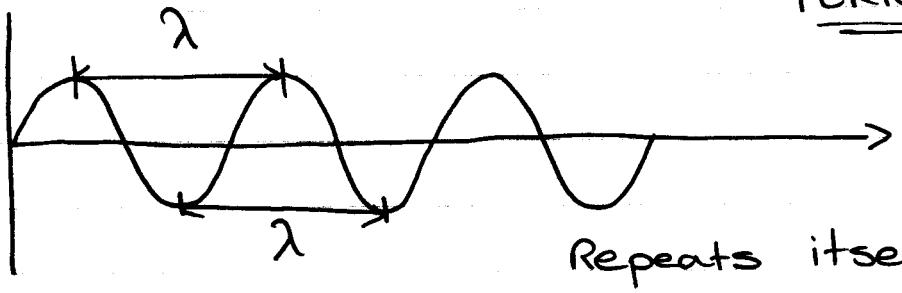
⇓

STRUCTURE

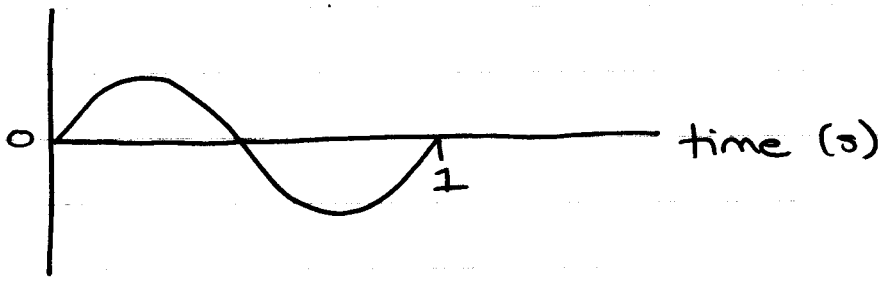
Consider waves:



PERIODIC

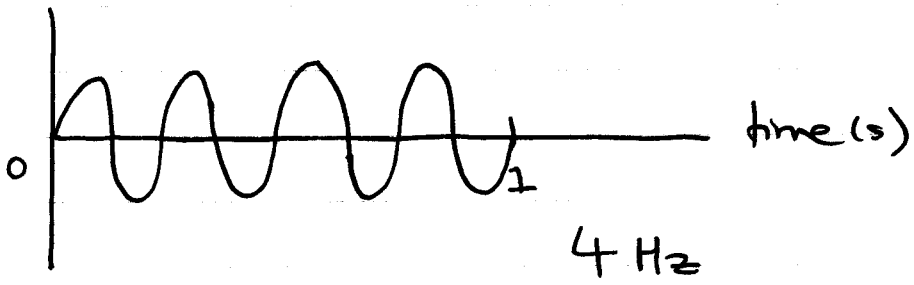



Frequency ($\nu$) nu




1 cycle per s
1 Hertz (Hz)

note NMR → MHz $10^6$ Hz




ENERGY (E) $\propto$ FREQUENCY ($\nu$)

$E = h\nu$ PLANCK'S CONSTANT
$9.537 \times 10^{-14}$ Kcal s $mol^{-1}$

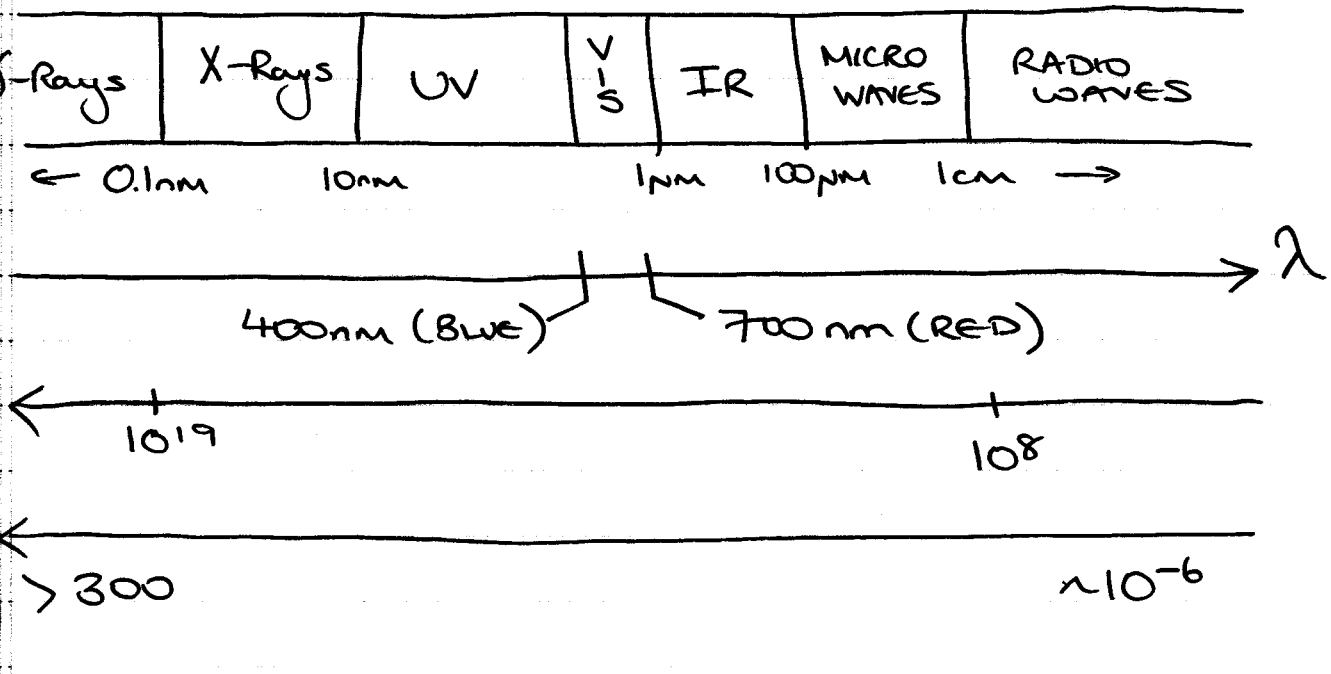
$c = \lambda\nu$ c = velocity of light $3 \times 10^8$ m/s

$\therefore \nu = c/\lambda$

$E = \frac{hc}{\lambda}$

so ENERGY $\propto$ 1/WAVELENGTH

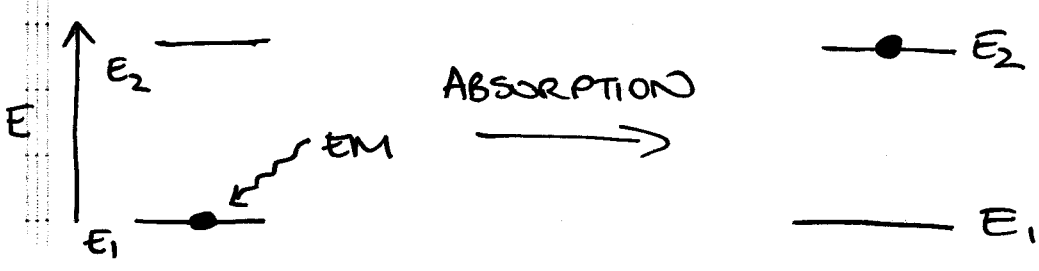
ELECTROMAGNETIC SPECTRUM



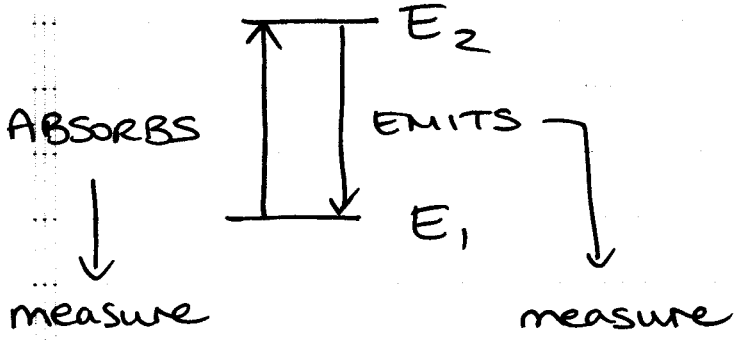

RADIATION of DIFFERENT ENERGIES → INVESTIGATE DIFFERENT ASPECTS OF STRUCTURE

QUANTIZATION of ENERGY

consider an atom / molecule



Transition is characteristic of the system i.e. H atom, $CH_3CH_2OH$ molecule etc




$E_2 - E_1$ gives an energy that corresponds to a given $\nu$ or $\lambda$, characteristic

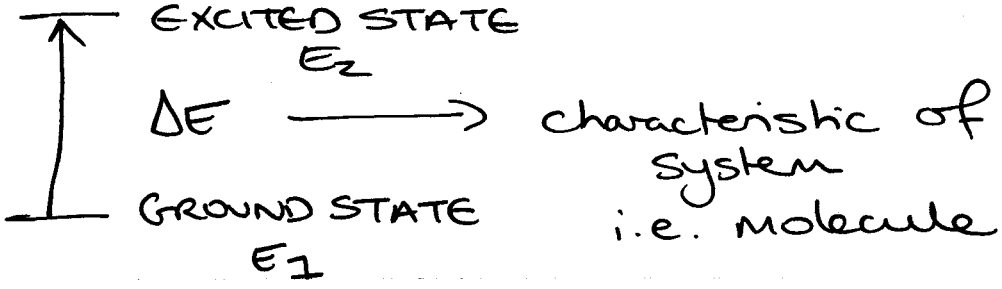
↓

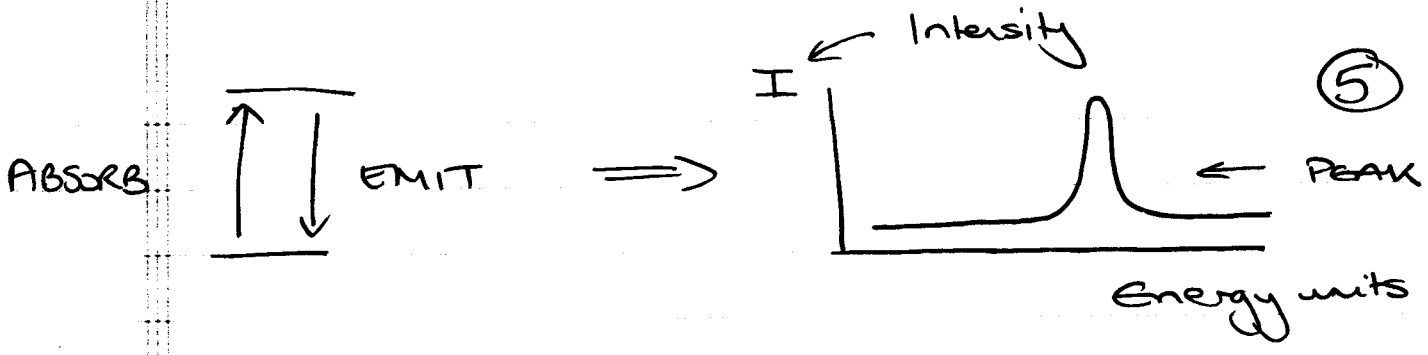
MOLECULAR STRUCTURE

Types of energy transitions

| Radiation | Transitions |
|---|---|
| UV-Vis | ELECTRONIC |
| IR | VIBRATIONAL |
| MICROWAVES | ROTATIONAL |
| RADIO (NMR) | NUCLEAR SPIN |

Any spec expt requires a transition between two energy levels






5

CONNECTIVITY

- NUCLEAR MAGNETIC RESONANCE (NMR)
- INFRA RED SPECTROSCOPY → FUNCTIONAL GROUPS
- MASS SPECTROMETRY → MOLECULAR FORMULA

not interaction w/ radiation

- UV/Vis Spectroscopy → CONJUGATION
- X-Ray crystallography

↓

precise atomic coordinates (WHY BOTHER w/ other methods?)

↓

ultimate in characterization

SOLID STATE vs SOLUTION

↑

Snapshot

X-rays are diffracted / scattered

↳ requires crystalline solids

↳ v. labor intensive relative to other techniques.

LEC (11)



(1) MIDTERM 1

LOW = 2, HIGH = 100, AVERAGE = 50

- READ THE QUESTIONS
- TEXAS CARBONS

(1) NMR Spectroscopy

THEORY

---

(1) NMR Spec → NUCLEAR MAGNETIC RESONANCE (absorption of radio frequency radiation by nuclei)

- most important spec technique in O-chem
- detect different nuclei in different environments

$CH_3CH_2-OH$ ⇒ 2 different C environments

↑ ↑ ↑

3 different H environments

$^1H$ NMR Spectroscopy

$^{13}C$ NMR Spectroscopy

HISTORY

- NMR PHENOMENON DISCOVERED IN 1946 (PHYSICS)
- 1952 NOBEL PRIZE
- ~1960s CHEMISTRY
- ~1980s BIOCHEM (proteins etc)
- ~1990s MEDICINE

⇓⇓

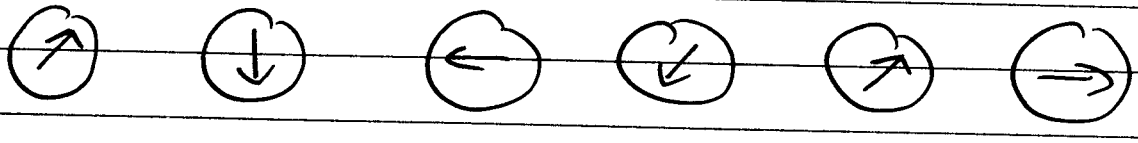
MRI (MAGNETIC RESONANCE IMAGING)

Word "nuclear" scares people.

---

NMR → MAGNETIC (strong magnetic field)

Imagine a compass, and pretend we can turn off the Earth's magnetic field.



random orientation - INCOHERENT

Turn field on → all align NORTH (lowest energy state)

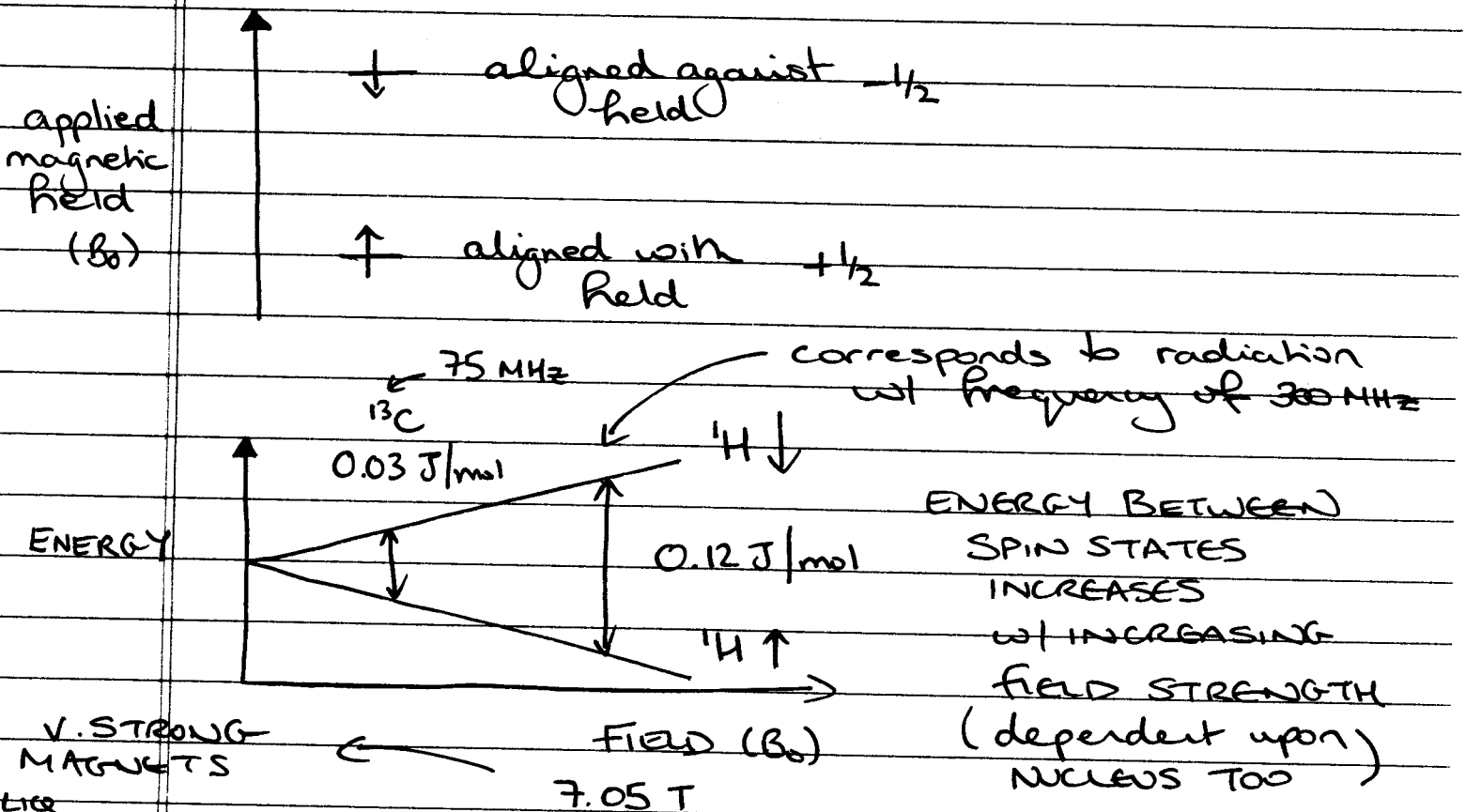
If we add energy (turn needle → SOUTH) if we let go it will spring back to NORTH

MOVE COMPASS TO AN INFINITE # of HIGHER ENERGY STATES, BUT ATOMS (NUCLEI) ARE QUANTIZED

NUCLEAR SPIN QUANTUM # I

# of SPIN STATES = $2I + 1$

most common $^1H$ and $^{13}C$ $I = 1/2$
(TWO SPIN STATES)




(Earth's magnetic field is $2 \times 10^{-5}$ T)

LIQ HELIUM 4.3K
LIQ $N_2$
VAC JACKET

[HARDER TO MOVE COMPASS NEEDLE IN A HIGHER FIELD]

# Relative Energies Between Transitions

NMR 0-1 J/mol
IR (vibrational energy levels) 10-60 kJ mol$^{-1}$
UV (electronic energy levels) 150-600 kJ mol$^{-1}$

- nuclear transitions ⇒ V. small energies

At 7.05 T, $^1H$ 25°C

$\Delta G = -RT \ln K_{eq}$

↳ $\Delta G = -2.303\, RT \log(N\downarrow / N\uparrow)$

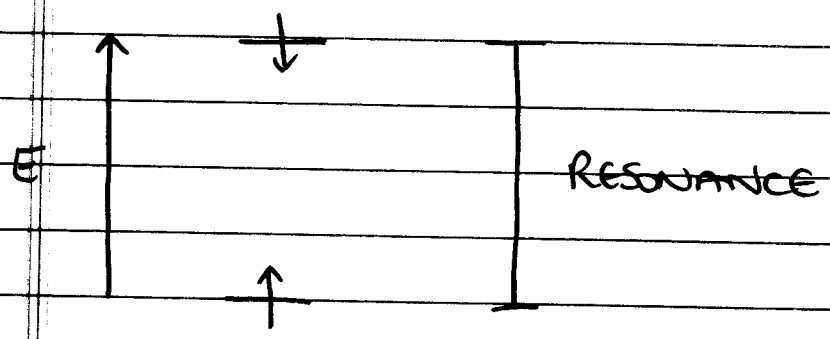
⇒ $\Delta G = 0.12$ J/mol

⇒ $N\downarrow / N\uparrow = 0.9999517 = \frac{1000000}{1000048}$

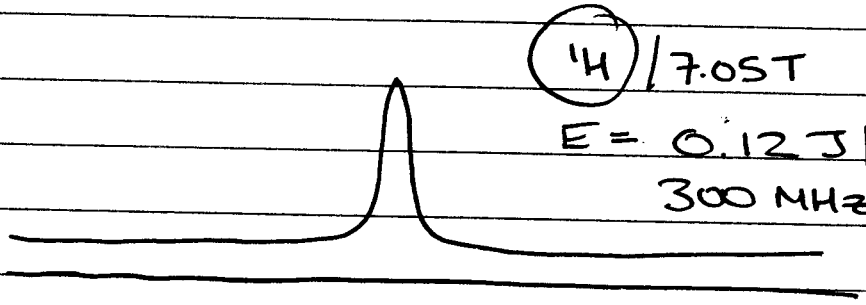
for every 1000000 H nuclei aligned against the field, there are 1000048 aligned with. (48 per million)

Strength of NMR signal ∝ population difference

↳ greater difference — stronger signal
⇒ more sensitivity



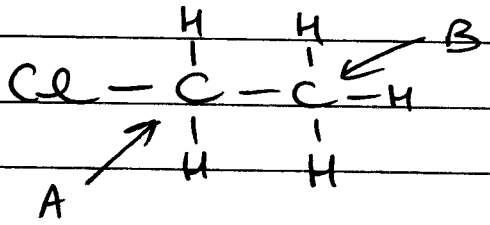

When irradiation frequency corresponds to the energy of the nuclear transition, energy is absorbed and the spin flips → the nucleus comes into resonance.

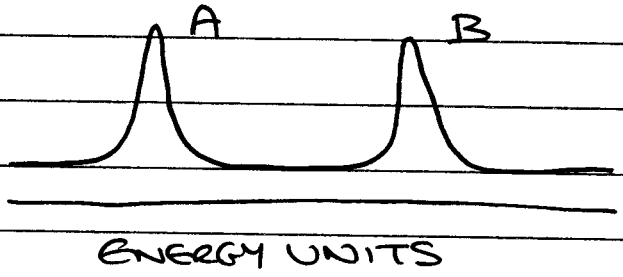



If ALL H atoms were the same (isolated from all other electrons and atoms) the signal would be the same for all H atoms. H atoms would be INDISTINGUISHABLE.

SAME FOR C ATOMS.

BUT WE DEAL W/ MOLECULES, SO ALL ATOMS ARE NOT NECESSARILY IN THE SAME ENVIRONMENT.



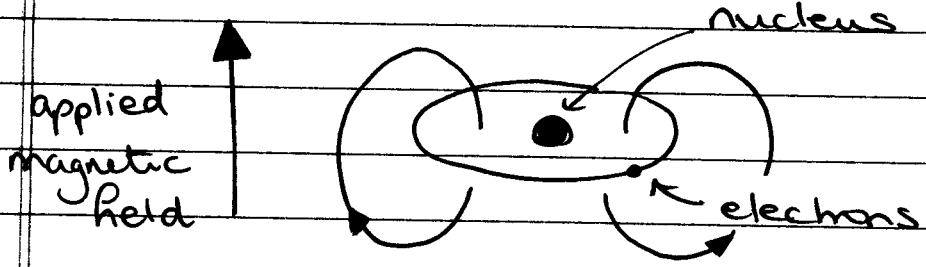




WHY?

Apply a field $B_0$

(C)

Each nucleus surrounded by an electron cloud which in magnetic field sets up a tiny current, which induces a magnetic field that opposes the applied magnetic field.




induced field shields nucleus

$B_{effective} = B_0 - B_{induced}$

↳ local field corresponds to modified energy gap between states → different frequency

So:

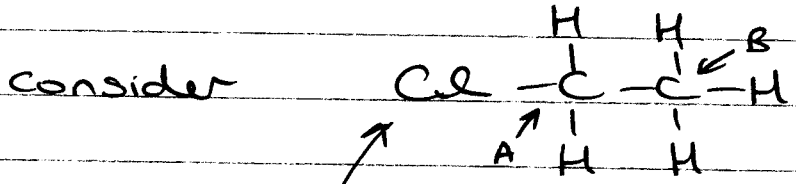
changes in distribution of electrons around a nucleus affect

(i) local magnetic field nucleus experiences
(ii) frequency at which nucleus resonates
(iii) chemistry of molecule at that atom

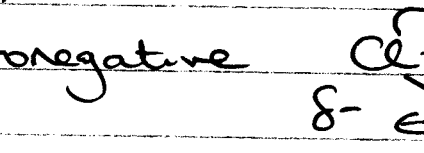
VARIATION in frequency known as

CHEMICAL SHIFT = $\delta$ (DELTA)

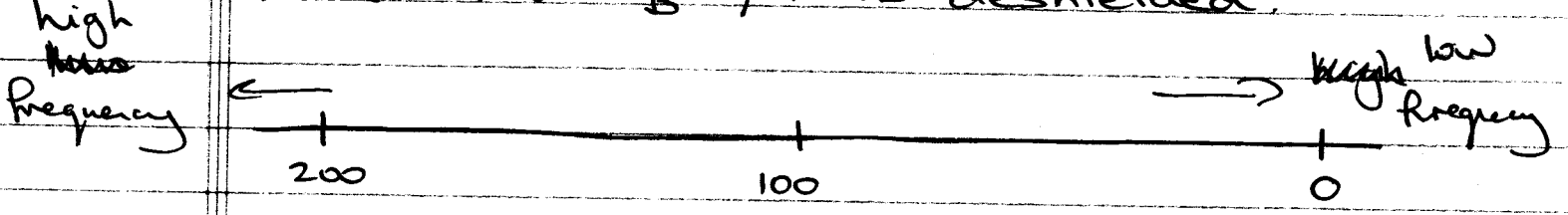
consider




more electronegative




So, magnetic field felt by $C_A$ is greater than that experienced by $C_B$ — $C_A$ is less shielded from the external applied field than $C_B$, it is deshielded.



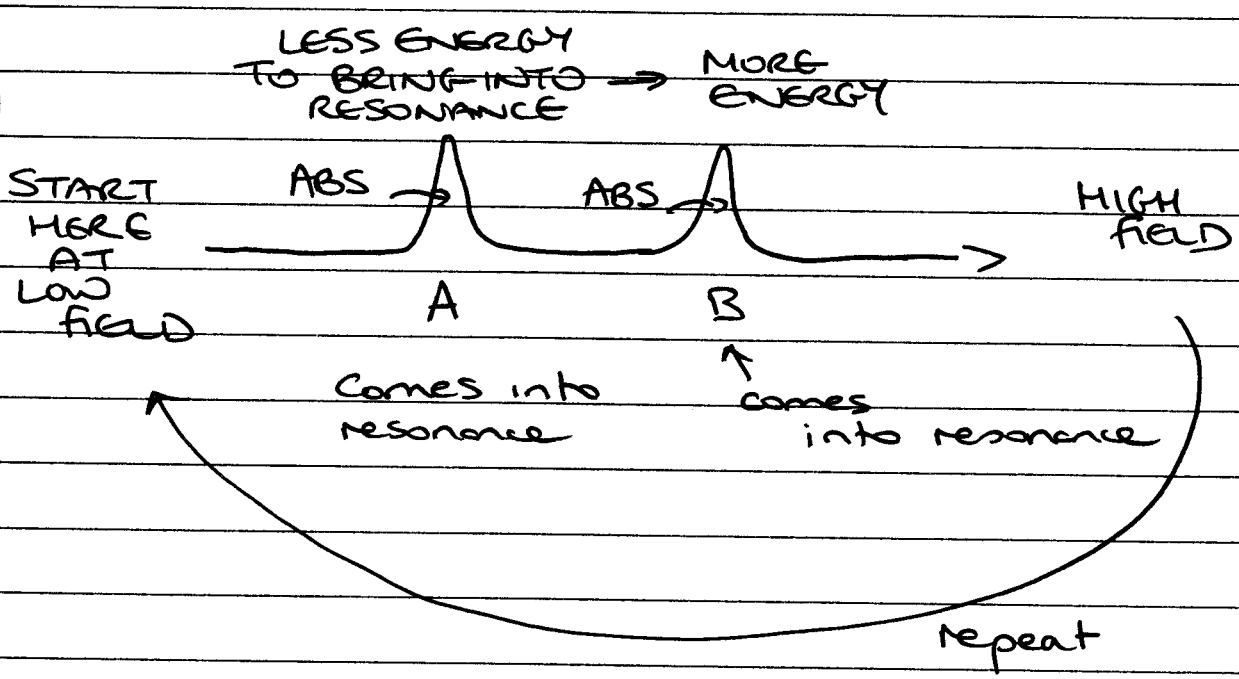

CHEMICAL SHIFT SCALE ($\delta$ SCALE)

(down field) low field
DESHIELDED

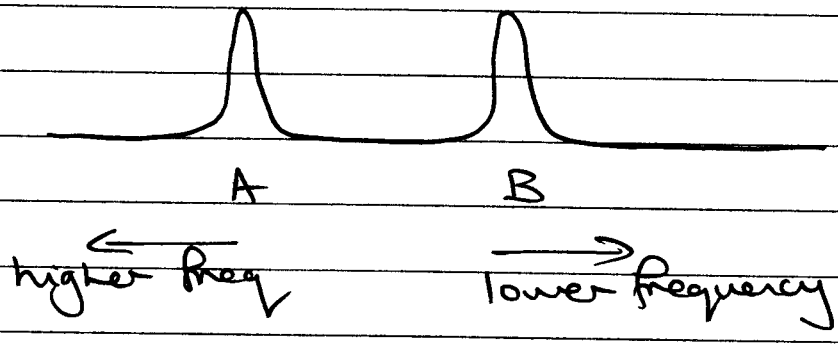
high field (upfield)
SHIELDED

LOW FIELD & HIGH FIELD —
relic from the days of
CONTINUOUS WAVE NMR

constant frequency, and scan field




At constant field, A feels more of the field, hence higher energy gap, and hence larger resonant frequency



NMR machines today —

SHORT $10^{-5}$ s

constant field → use an $R_f$ pulse, range of frequencies, excites all nuclei, and then as they relax back to the low spin state the energy given out is detected by what is essentially a sophisticated radio receiver

↳ results are deconvoulted
FOURIER transformed to give a spectrum

CHEMICAL SHIFT SCALE
not in magnetic field units
not in frequency units,

but ppm parts per million

CHEMICAL SHIFT $\delta$

$$\delta = \frac{\text{frequency (Hz)} - \text{frequency TMS (Hz)}}{\text{frequency TMS (MHz)}}$$

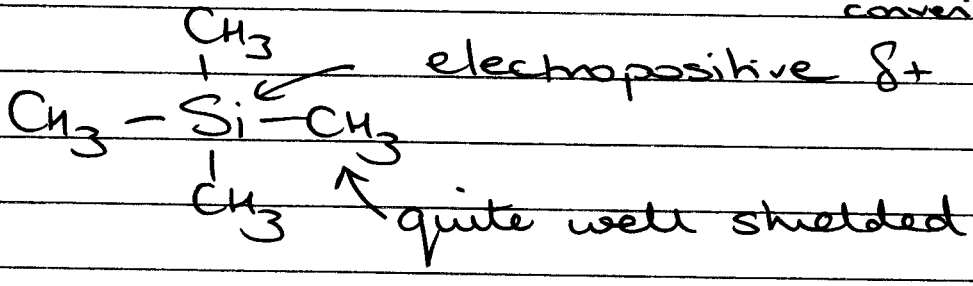
APPLIED MAGNETIC FIELD ~300 MHz (7.05T)

NOT EXACTLY CONSTANT FROM MACHINE TO MACHINE...

⇒ INERT SOLUBLE IN ORGANICS

TMS = Tetramethylsilane (STRONGLY SHIELDED so most δ values are conveniently -ve)

SINGLE STRONG RESONANCE ↑ 12 IDENTICAL PROTONS




← electropositive δ+

↑ quite well shielded

C atom in TMS defined as zero ppm

(put back into equation)

BY DEFINITION is ZERO

e.g. $C_A - Cl$

On a 100 MHz machine

$$\frac{C_A \quad TMS}{100{,}005{,}000 - 100{,}000{,}000} = \frac{5000}{100\,MHz}$$
$$100\,MHz$$

$$= 50\ ppm$$

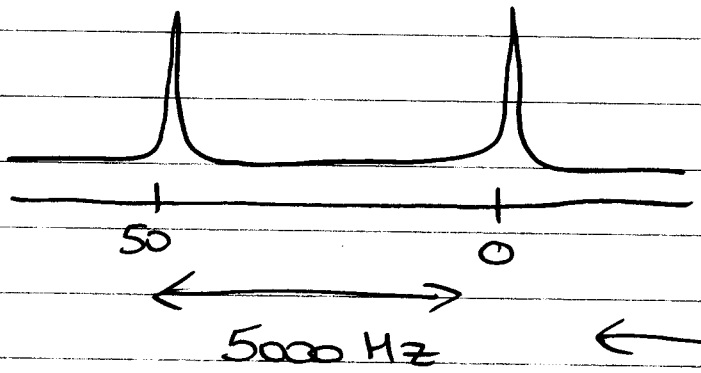
On a 50 MHz machine

$$\frac{C_A \quad TMS}{50{,}002{,}500 - 50{,}000{,}000} = \frac{2500}{50\,MHz}$$
$$50\,MHz$$

$$= 50\ ppm$$

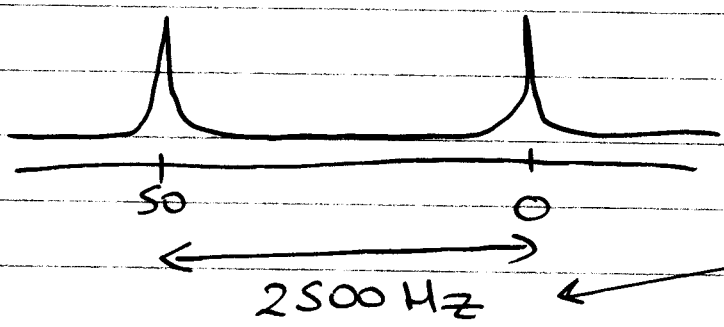
50 ppm on each machine, but:

100 MHz




different T values too

50 MHz

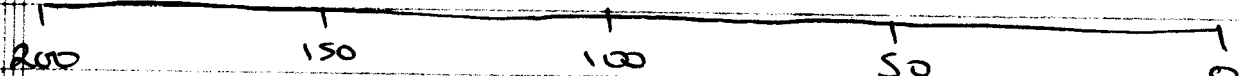



TMS chosen, as most other C atoms come between 0-200 ppm

Also, one "100 MHz" machine may be "100.1 MHz, and another may be 99.9. Using a ratio to a standard compound makes this not a problem.

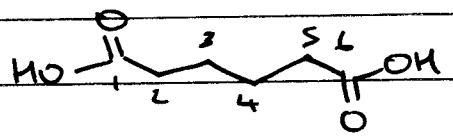
---

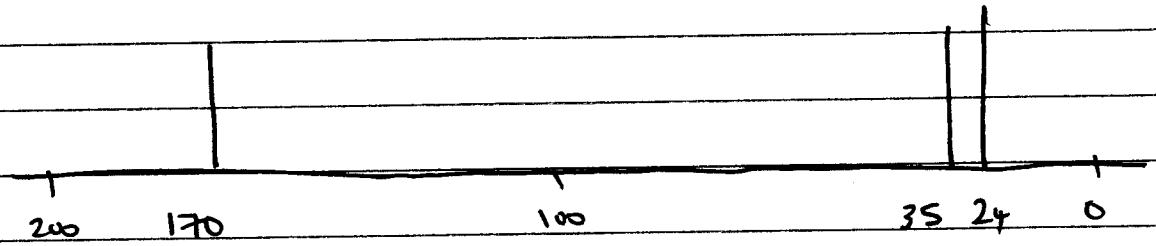
REGIONS OF $^{13}C$ NMR SPECTRUM



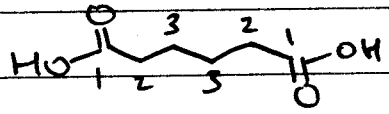

| Unsaturated C atoms next to O | Unsaturated C atoms | Saturated atoms next to oxygen | Saturated C atoms |
|---|---|---|---|
| C=O | C=C & aromatic | $CH_3O$, $CH_2O$ | $CH_3$, $CH_2$, CH |

HEXANEDIOIC ACID



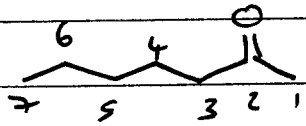




ONLY 3 signals WHY

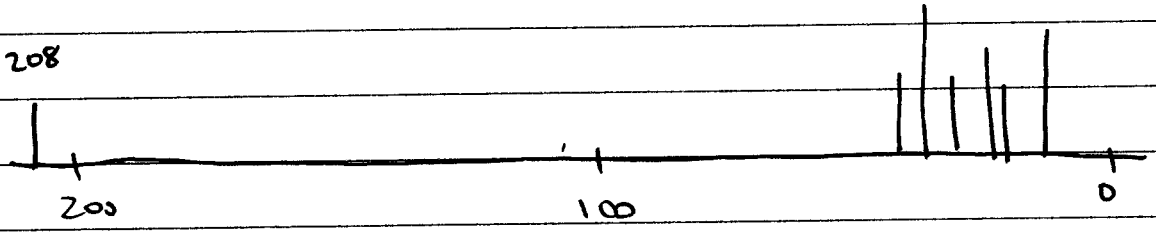



SYMMETRY

HEPTAN-2-ONE




0-50ppm




NO SYMMETRY, ⇒ 7 signals

LEC (12) 

(1) No CNSI Lecture Tuesday
(2) HMK
13.8, 13.9, 13.14–17

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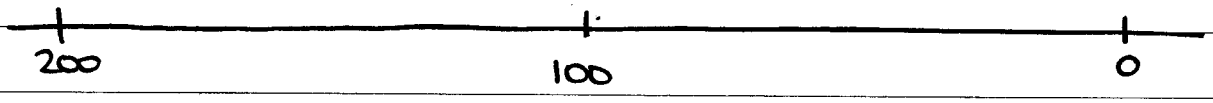
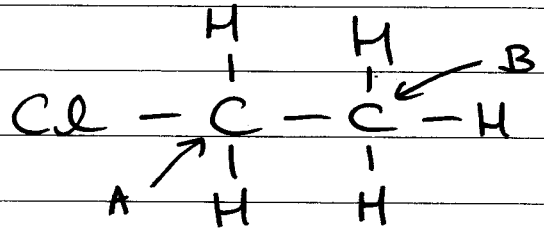
(1) Intro cont...
(2) $^{13}C$ NMR Spec

---

δ SCALE $^{13}C$



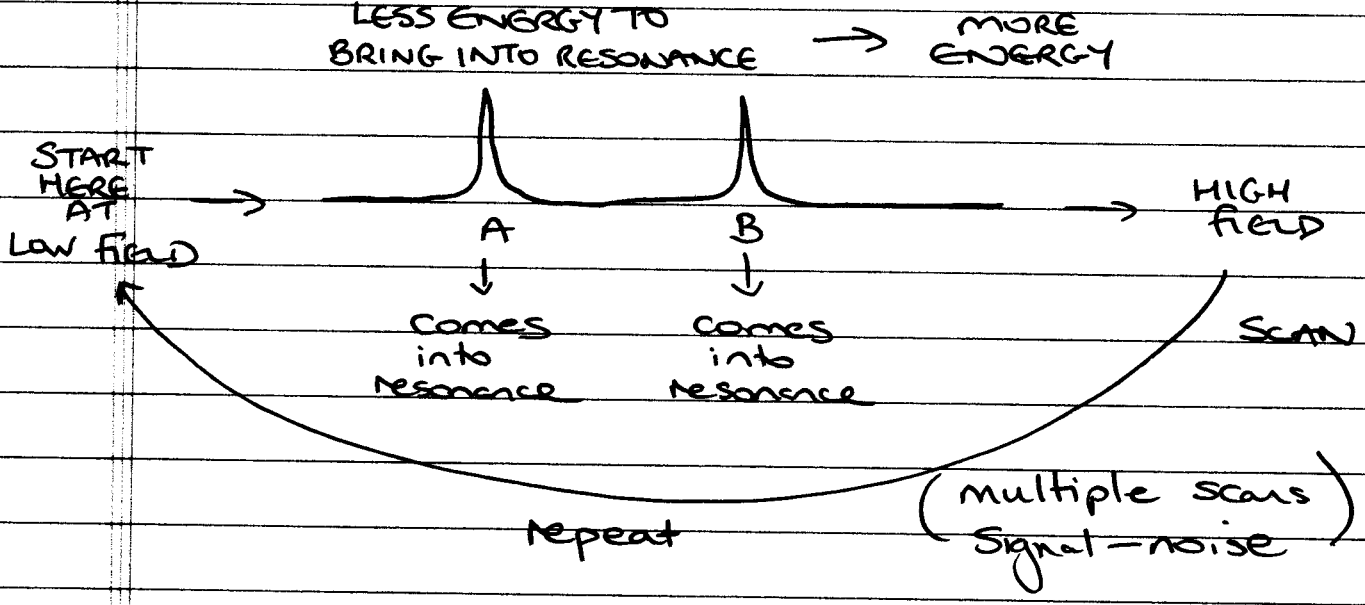

← high frequency — low frequency →
← low field (downfield) — high field (upfield) →
← deshielded — shielded →



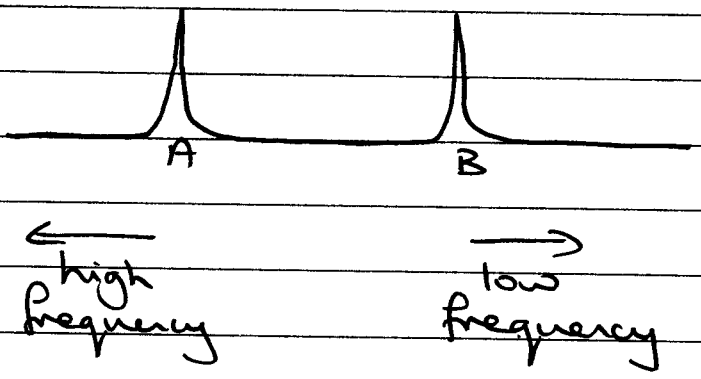
Low field & High field

↳ RELIC from days of CONTINUOUS WAVE NMR

constant frequency and <u>scan</u> field




However, at constant field, A feels more of the field than B, hence a higher energy gap between ↑ and ↓ and thus a larger resonant frequency.



# NMR Machines today

CONSTANT FIELD, SHORT ($10^{-5}$ s) $R_F$ PULSE

- excites all susceptible nuclei
- relax back to low-spin state

↓

all nuclei emit and is detected by what is essentially a sophisticated radio receiver

↳ jumble of signals undergo a FOURIER TRANSFORM (mathematical process) to deconvolute into a spectrum

---

CHEMICAL SHIFT SCALE

- not in magnetic field units
- not in frequency units

but in ppm (parts per million)

CHEMICAL SHIFT $\delta$

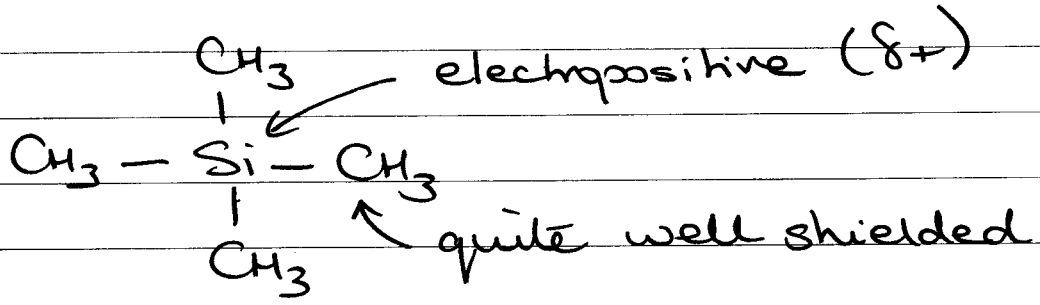
$$\delta = \frac{\text{frequency (Hz)} - \text{frequency TMS (Hz)}}{\text{frequency TMS (MHz)}}$$

APPLIED MAGNETIC FIELD ~7.0ST ($^1H$ = 300 MHz)

NOT EXACTLY CONSTANT FROM MACHINE TO MACHINE

NEED A STANDARD

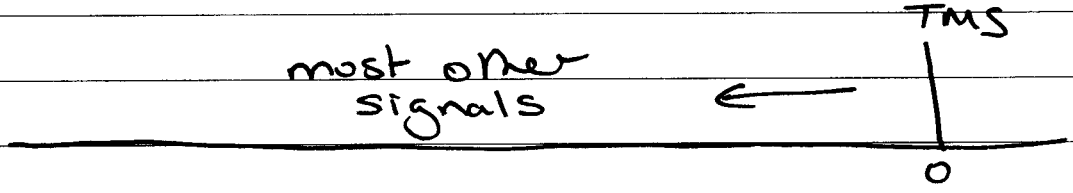
TMS = Tetramethylsilane




- INERT
- SOLUBLE IN ORGANICS
- SINGLE STRONG RESONANCE
  12 identical PROTONS, 4 IDENTICAL CARBONS

C ATOM
H ATOM
} DEFINED AS 0 ppm by DEFINITION

STRONGLY SHIELDED so most other δ values are conveniently positive




Put back into equation:

e.g. $C_A - Cl$

On a 100 MHz machine

$$\frac{C_A \quad TMS}{\frac{100,005,000 - 100,000,000}{100\ MHz}} = \frac{5000}{100\ MHz}$$

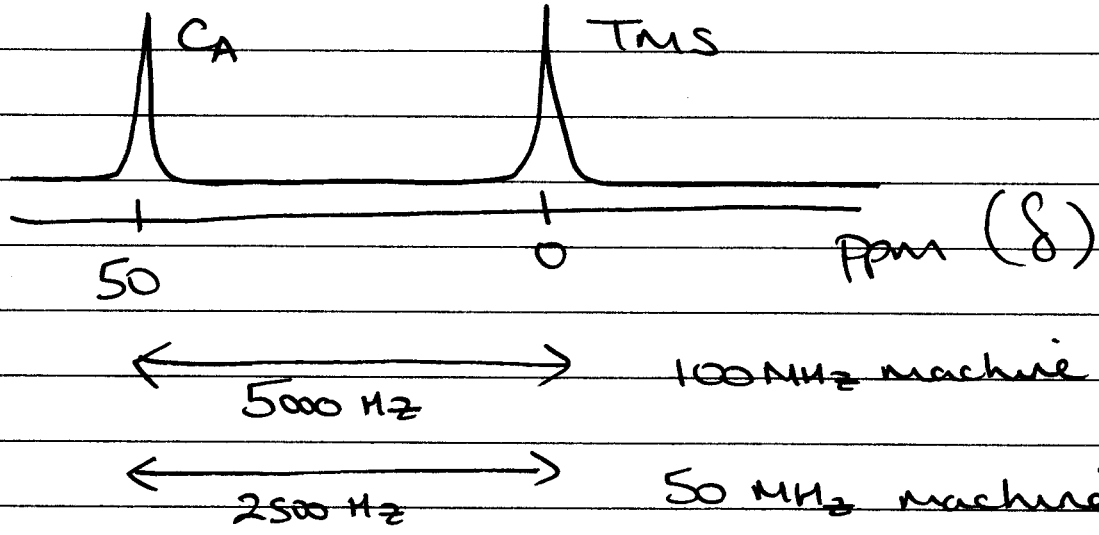
$$= 50\ ppm$$

On a 50 MHz machine

$$\frac{50,002,500 - 50,000,000}{50\ MHz} = \frac{2500}{50\ MHz}$$

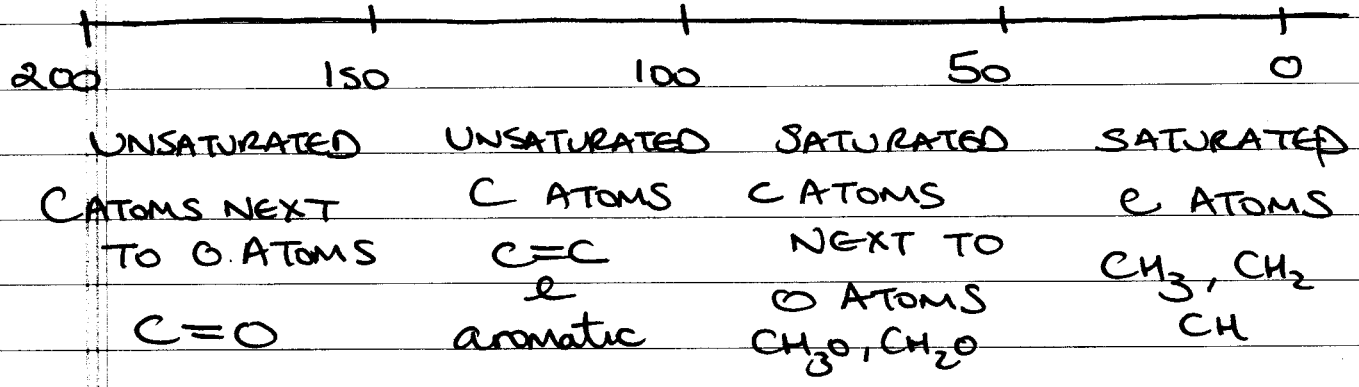
$$= 50\ ppm$$

50 ppm on each machine), but



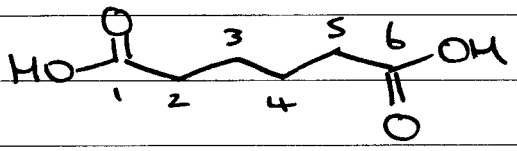

Also "100 MHz" machine is not necessarily 100 MHz, may be 100.1 MHz or 99.9 MHz, using a ratio to a standard makes this not a problem.

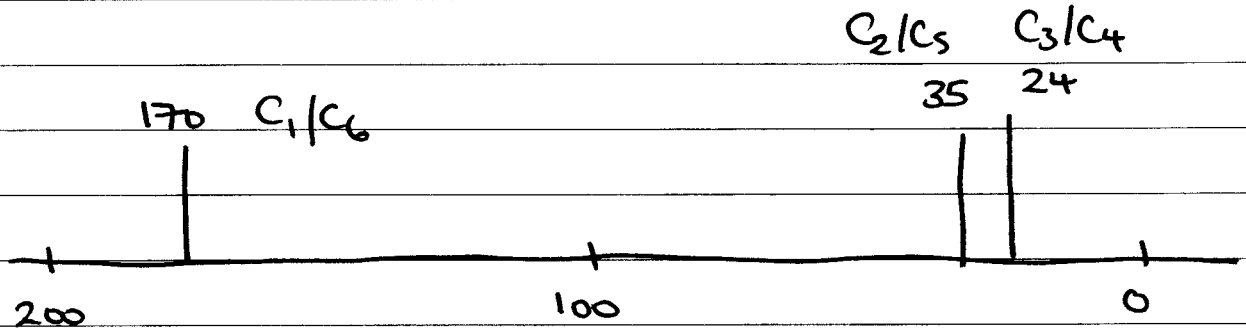
# REGIONS of $^{13}C$ NMR spectra



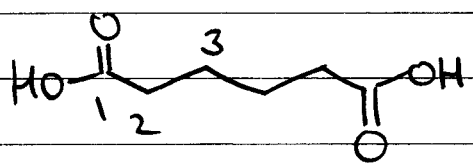

EXAMPLES (PROTON DECOUPLED ⟹ EXPLAIN WHAT THIS MEANS LATER)

HEXANEDIOIC ACID



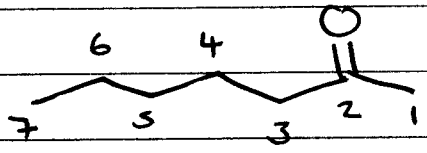



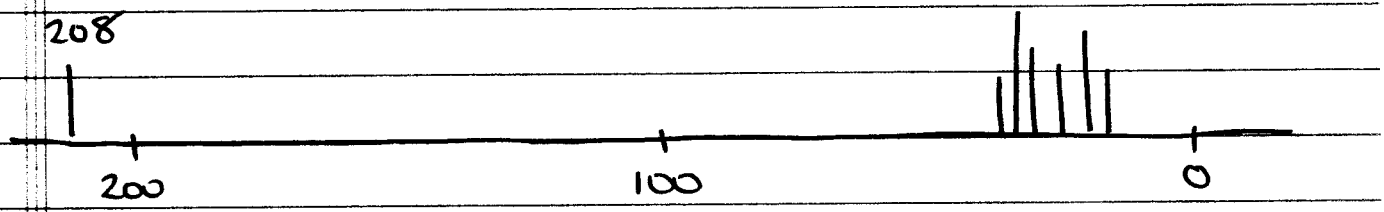

ONLY THREE SIGNALS




SYMMETRY

HEPTAN-2-ONE

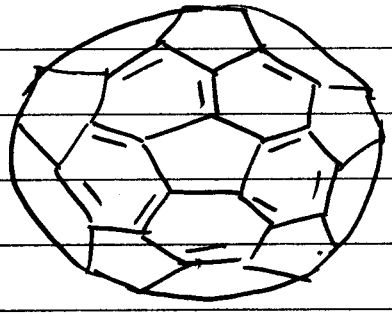


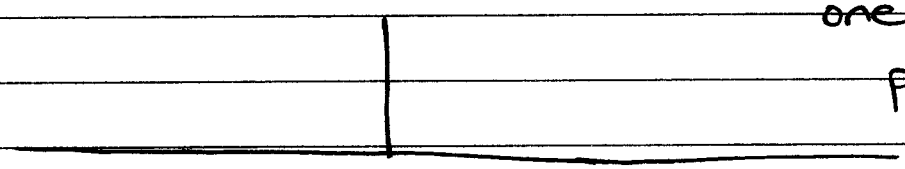

NO SYMMETRY ⇒ 7 SIGNALS, one for each C atom

EACH UNIQUE CARBON ATOM GIVES RISE TO A SINGLE ~~13C~~ PEAK IN THE $^{13}C$ NMR SPECTRUM.

e.g.



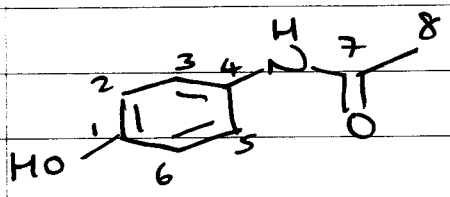
$C_{60}$

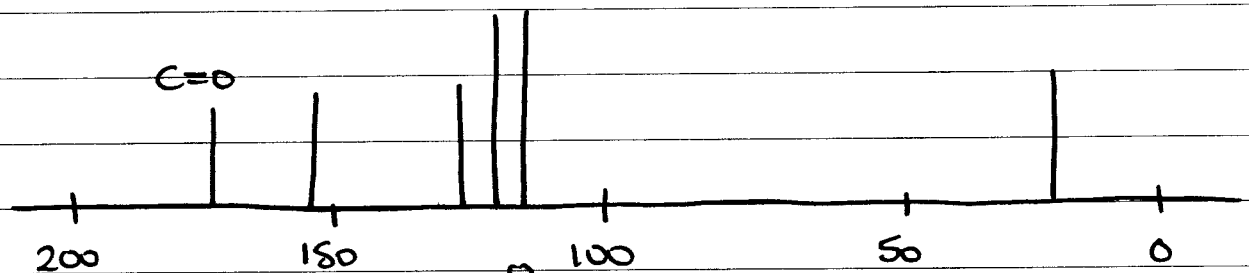


one single peak.

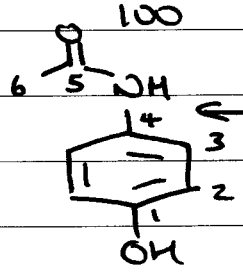
~ 142 ppm

# TYLENOL (ACETOMINOPHEN)




6 peaks




← fast rotation

$C{=}O$ 168 ppm
$C_1$ (C–O) 153 ppm
$C_6$ 24 ppm saturated

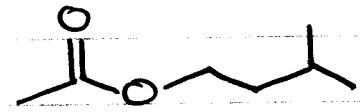
$^{13}C$ is only 1.1% abundant ($^{12}C$ NMR silent)

⇒ WEAK SIGNAL
(MANY SCANS)

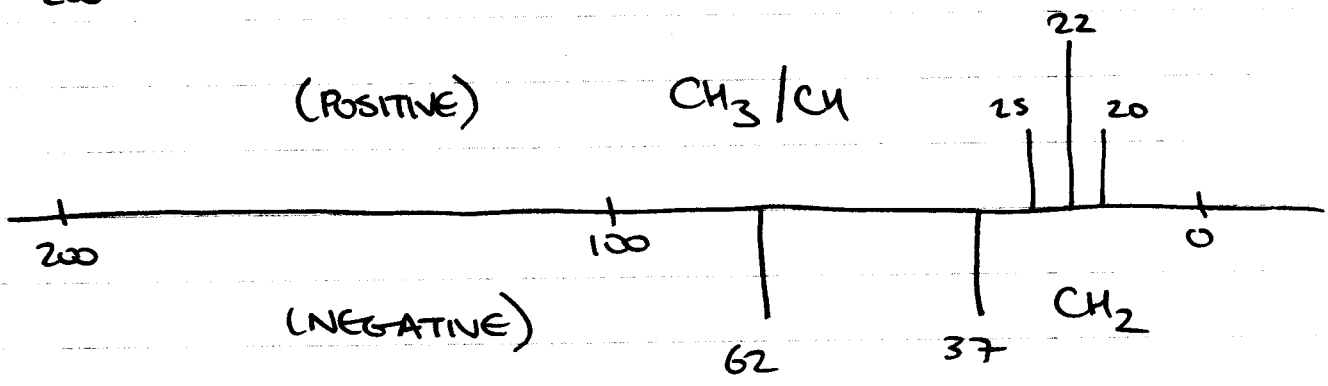
---

DEPT — good way of distinguishing
C, CH, $CH_2$, $CH_3$
(HOW MANY H ATOMS C IS BONDED TO)

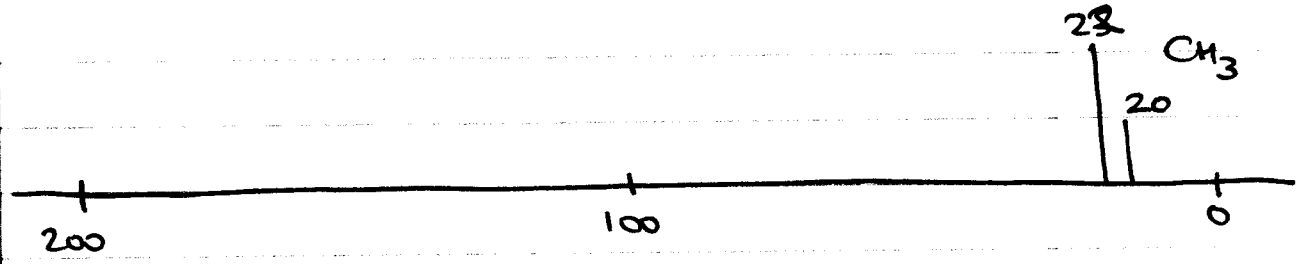
# Isopentylacetate



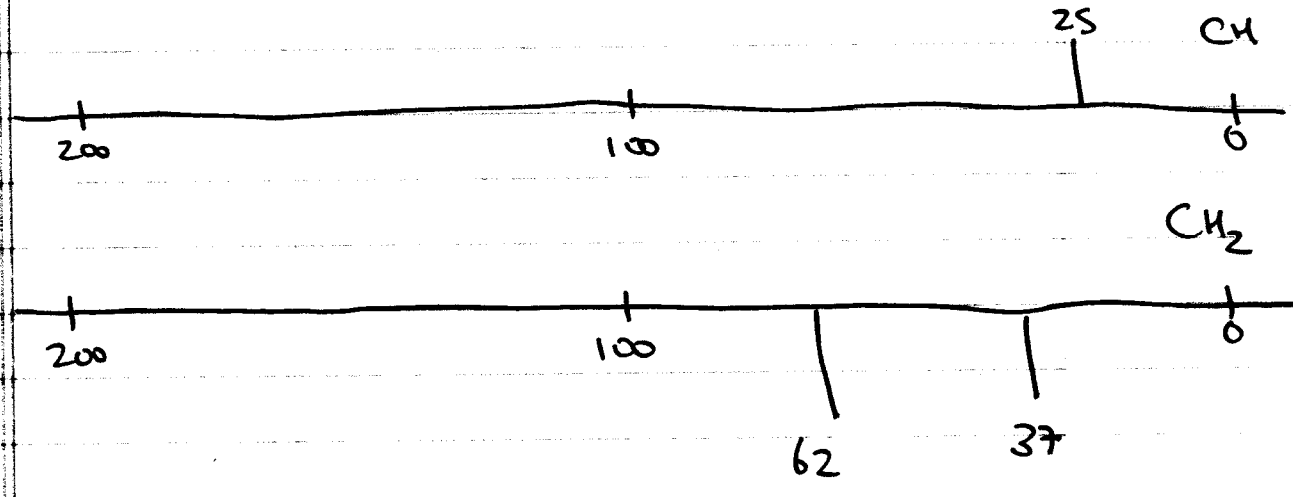


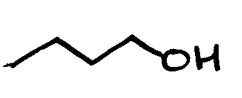
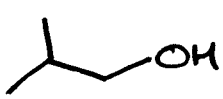
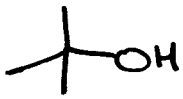




QUAT C do not SHOW UP




SWITCH



ALCOHOLS $C_4H_{10}O$   

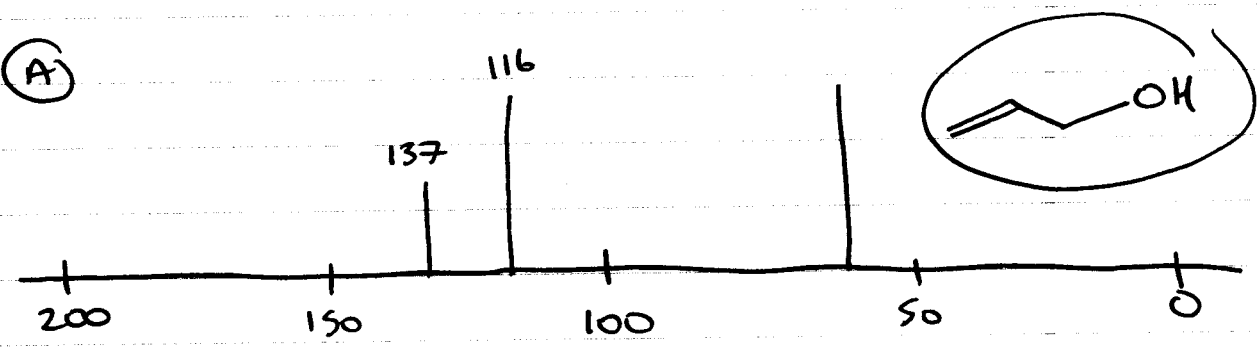
4 signals 3 signals 2 signals

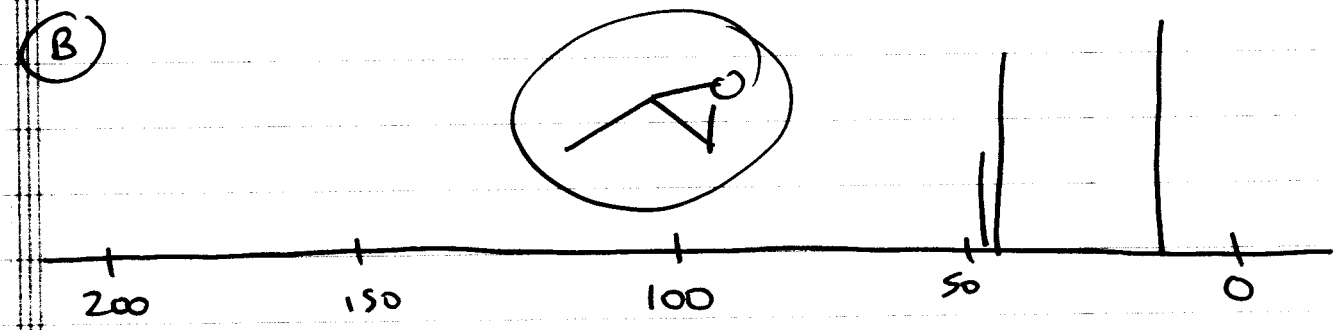
10

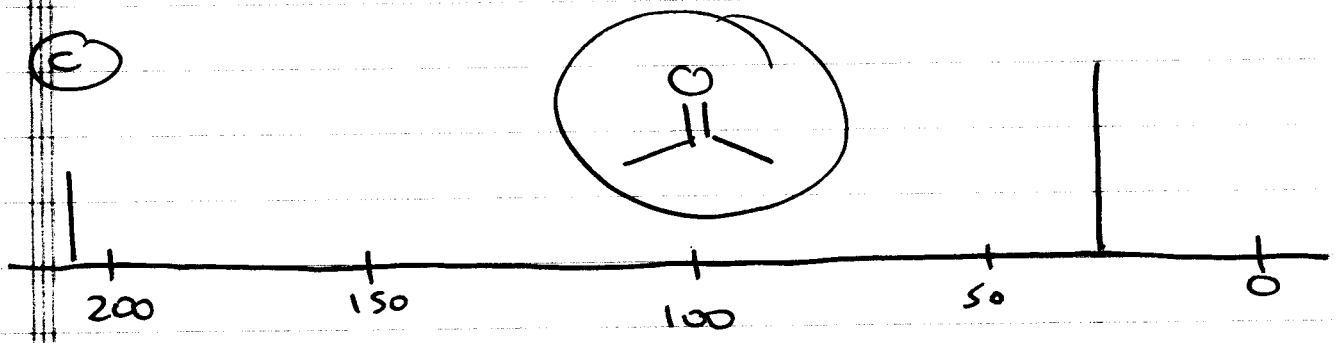
$C_3H_6O$

⇓

Seven reasonable structures

A) 


B) 


C) 


INTENSITY of SIGNALS — NOT SO MEANINGFUL IN $^{13}C$

Cquat not so INTENSE

LEC 13 

(1) HMK: Handout + Same problems as last time (13.8, 9, 14–17)

13.2, 3, 4, 5, 6, 18, 19, 20

---

(1) $^{13}C$ NMR
(2) $^{1}H$ NMR

(1) $^{13}C$ NMR

- ONLY 1.1% ABUNDANT ($^{12}C$ NMR Silent, I=0)
  → Weak signals ⇒ many scans

Compare to $^{1}H$ NMR >99.9% abundant

- PEAK INTENSITY not really that MEANINGFUL → compare to $^{1}H$ ⇒ very important.

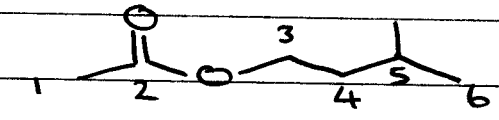
DEPT → Special Pulse sequence (2)

⇒ C–H connectivity

Distinguishes $CH_3$ from $CH_2$ from CH from $CH_0$

↑ quaternary C or carbonyl C

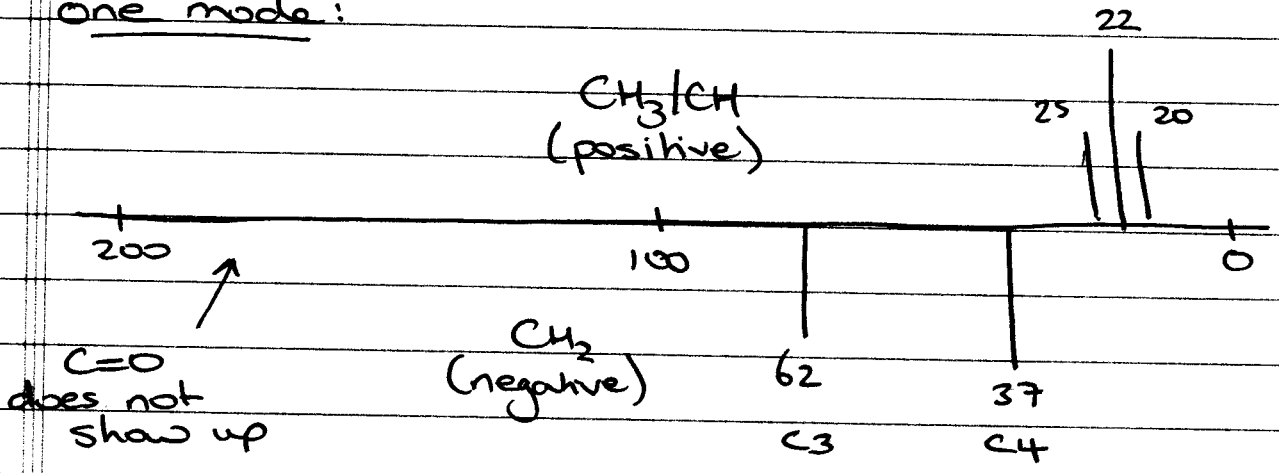
Consider: Isopentyl acetate

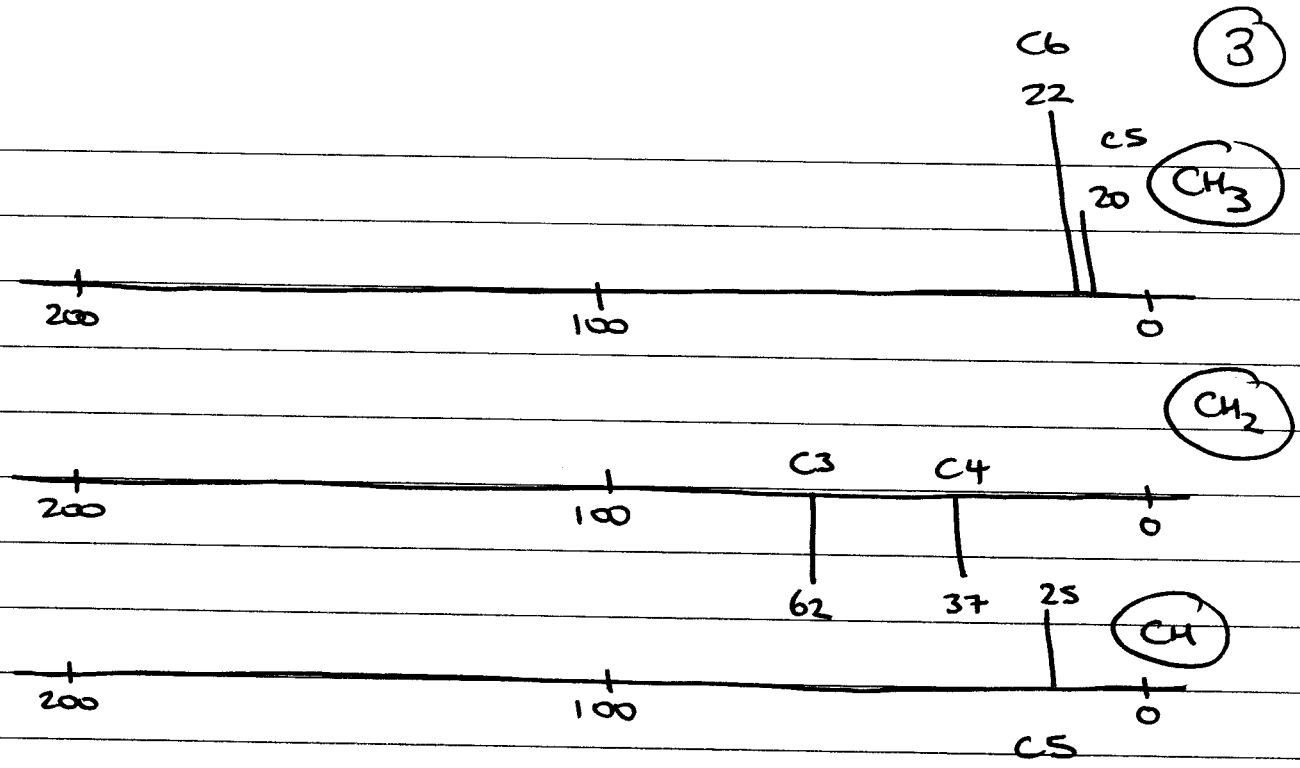




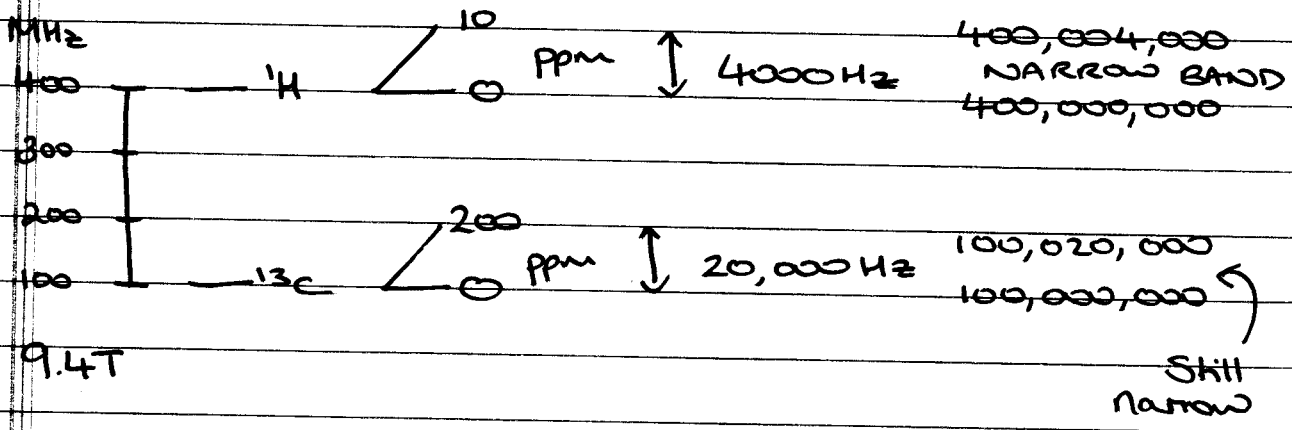


one mode:






$^1H$ NMR

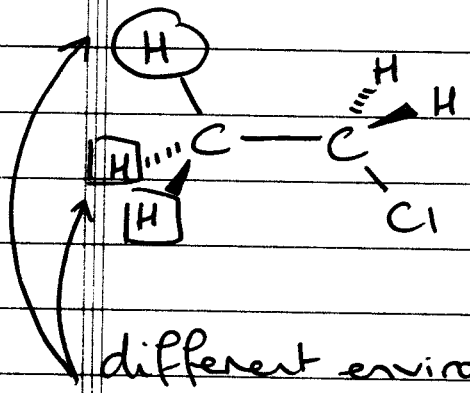



DO NOT GET OVERLAPPING SPECTRA FROM DIFFERENT NUCLEI.

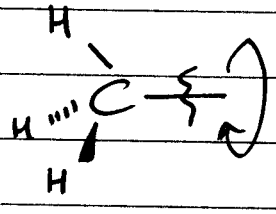
FUNDAMENTALLY, each UNIQUE PROTON gives one signal (like carbon)*

* more detail later

(i) (a) (b)
$CH_3CH_2Cl$ 2 signals

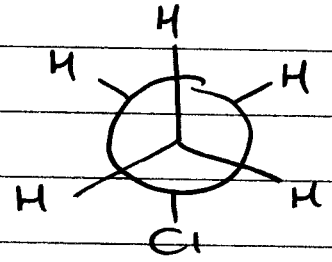


different environments



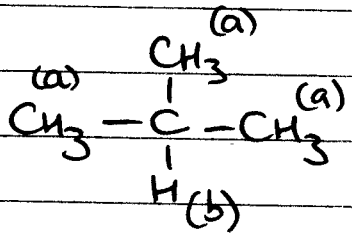
FAST ROTATION

TIME AVERAGED SIGNAL

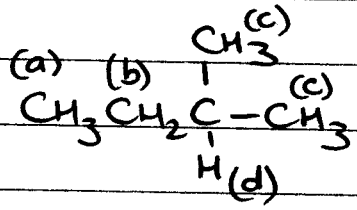


NEWMAN PROJECTION

NMR → camera w/ slow shutter speed

(ii)


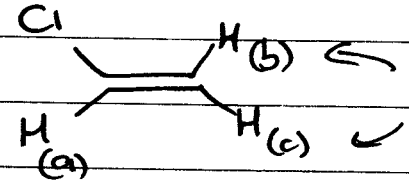
2 signals

(iii)


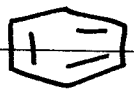
4 signals

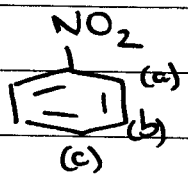
(iv) (a) (b) O (b) (a)
$CH_3CH_2CCH_2CH_3$ 2 signals

(v) (a) (b) O (c) (d)
$CH_3CH_2COCH_2CH_3$ 4 signals

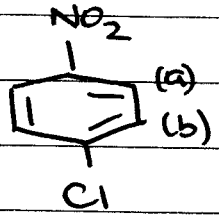
(vi) 

different
no rotation about C=C.

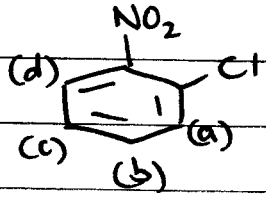
(vii)  → 1 signal

(viii) 

→ 3 signals

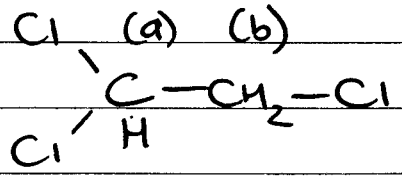
(ix) 

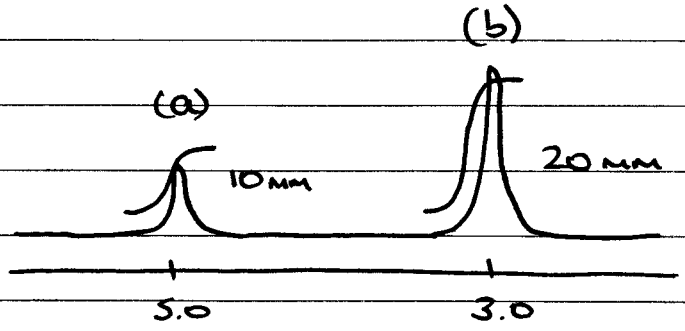
→ 2 signals

(x) 

→ 4 signals

- SIGNAL INTENSITY




- CHEMICAL SHIFT INFO

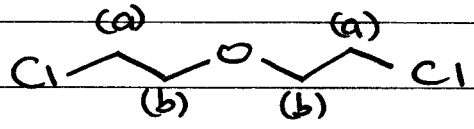
(a) on C with 2 Cl atoms
(b) on C with 1 Cl atom

INTEGRATION → AREA under curve

⇒ relative ratio of protons

1 : 2

just ratio, need molecular formula (MASS SPEC) to get structure, i.e.:

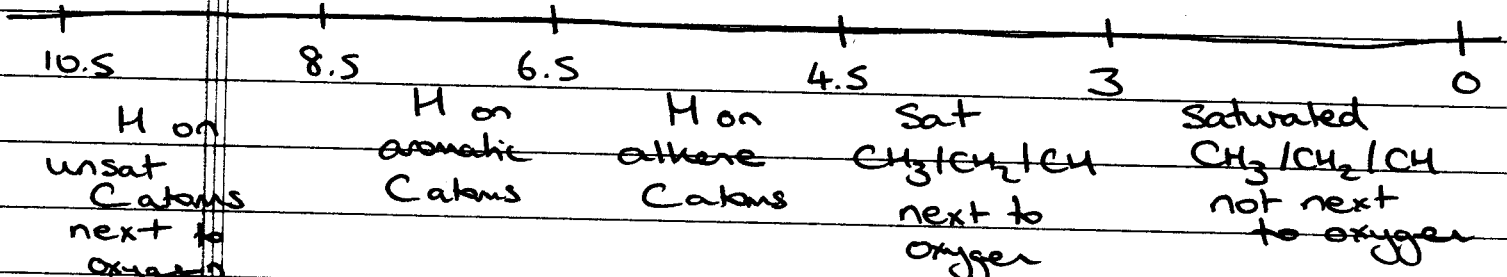




1:1 ratio, but 8 protons

# Chemical Shift

## H atoms on CARBON




e.g $H-C(=O)-C$

## Protons attached to N, O

ALCOHOLS $R-\underset{H}{O}$ 1–6 ppm

AMINES $R_2-\underset{H}{N}$ 1–6 ppm

PHENOLS $Ar-\underset{H}{O}$ 4–8 ppm

CARBOXYLIC ACIDS $RCO_2H$ 9–13 ppm

PROBLEM: APPROXIMATE RANGES

⇓

DIFFERENT BOOKS GIVE SLIGHTLY DIFFERENT VALUES!

## ELECTRONEGATIVITY EFFECTS

$CH_3-H \sim 1$

$ClCH_2-H \sim 3$

$Cl_2CH-H \sim 5$

$Cl_3C-H \sim 7$

ppm ↓ additive

## PROXIMITY

$HCH_2O$+ ~4 TWO BONDS

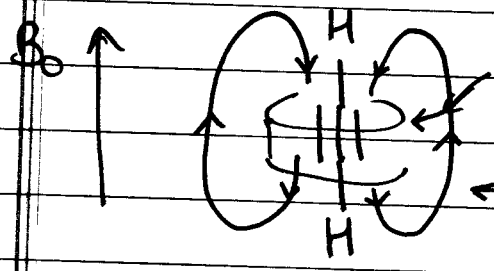
$HCH_2CH_2O$+ ~2.5 THREE BONDS

### Different Heteroatoms

| Electronegativity | | |
|---|---|---|
| 1.0 | $CH_3Li$ | −2 ppm |
| 1.9 | $CH_3Si(CH_3)_3$ | 0 ppm (BY DEFINITION) |
| 3.0 | $CH_3NH_2$ | 2.4 ppm |
| 3.4 | $CH_3OH$ | 3.5 ppm |
| 4.0 | $CH_3F$ | 4.3 ppm |

## π-BONDS

### ALKYNES

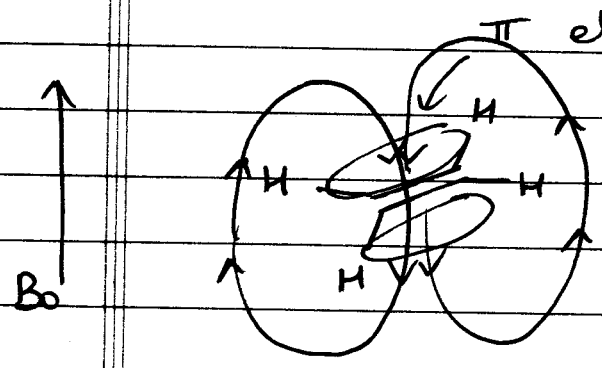



π electrons

← induced magnetic field IN REGION OF $H_s$, against applied field

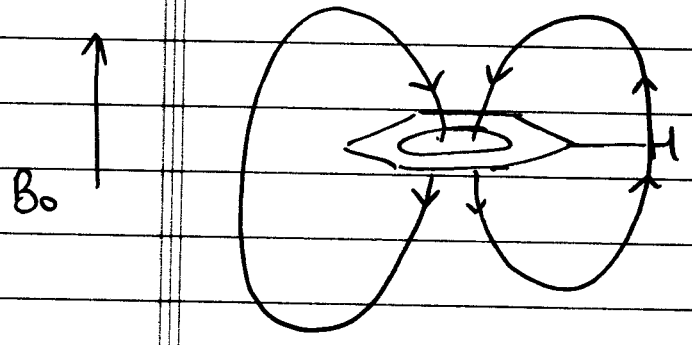
Hs are shielded (SMALLER PPM value than expected $\delta = 2-3$ ppm)

## ALKENES




In region of Hs, induced field reinforces applied field → experience a higher effective field than expected → resonate at higher frequency $\delta = 4.5 - 6.5$

## BENZENE RINGS

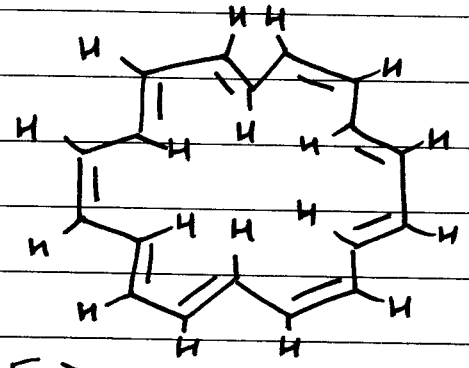



again, reinforces applied field
$\delta = 6.5 - 8.5$

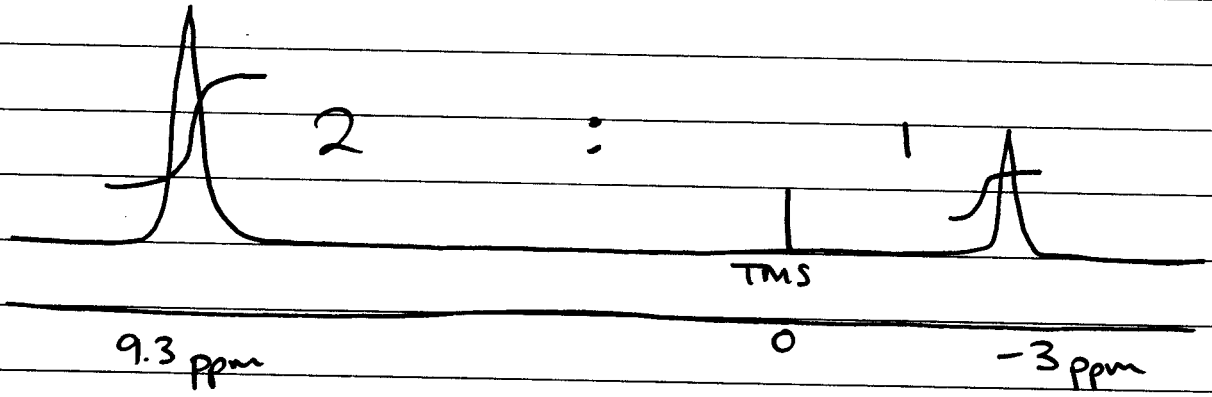
bigger than for C=C, because RING CURRENT

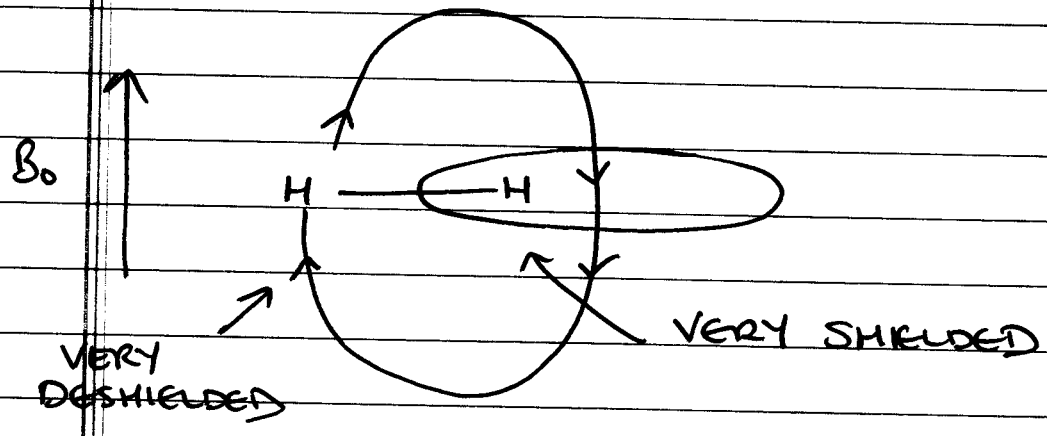
(not just 1 π bond, but 3π bonds
↳ delocalized)

# ANNULENES



[18] ANNULENE



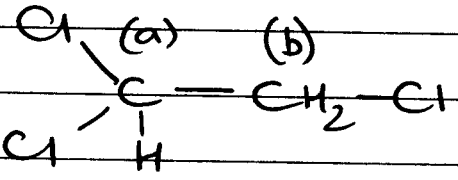




WHAT WE CAN DO SO FAR:

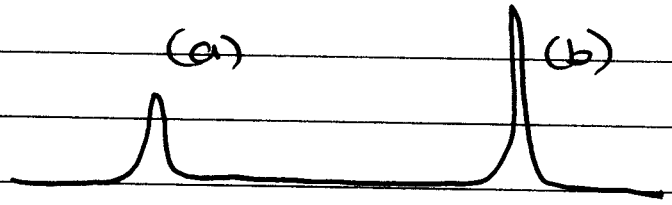
1. # OF SIGNALS => # OF SETS OF EQUIV H
2. INTEGRATION => RELATIVE H RATIOS
3. CHEMICAL SHIFT => LOCAL CHEMICAL ENVIRONMENT

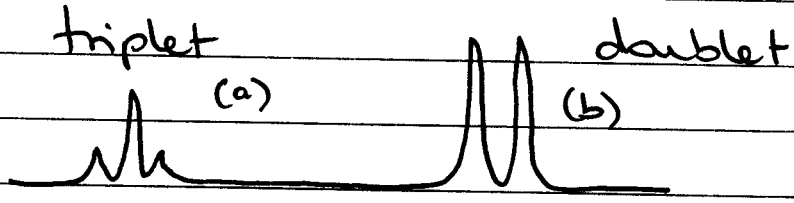
# Splitting Rule





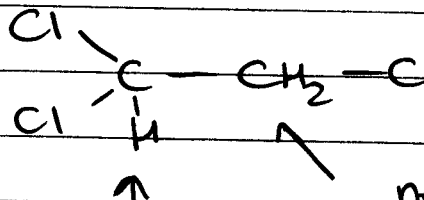

Signals split




degree of splitting $(n+1)$ rule

Count # of non equivalent Hs on adjacent C atoms:



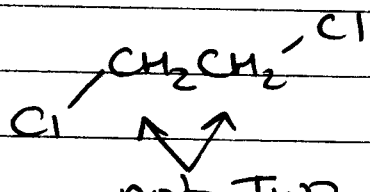

next to a C atom with 2 Hs

TRIPLET

next to a C atom with 1H

⇓

doublet

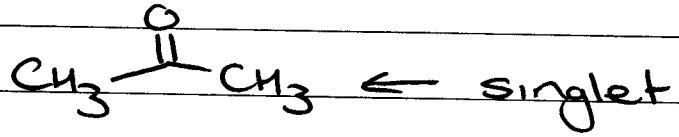


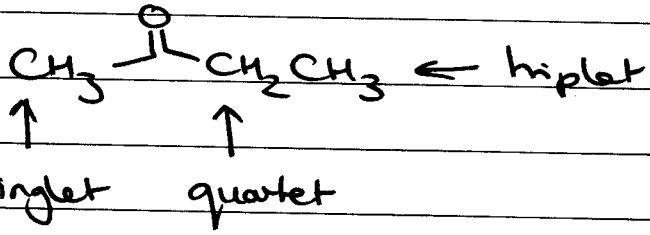

not TWO TRIPLETS

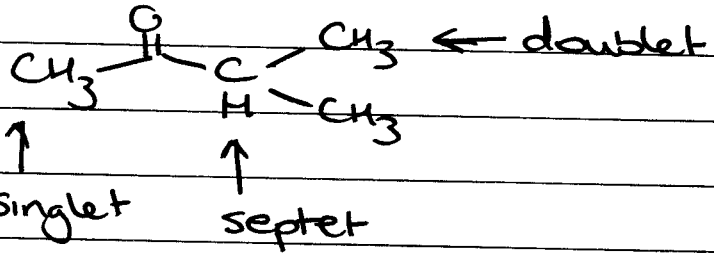
⇓

ONE SINGLET

e.g.




WHERE DOES THIS COME FROM?

(1) HMH 13.6, 13.21 – 13.30

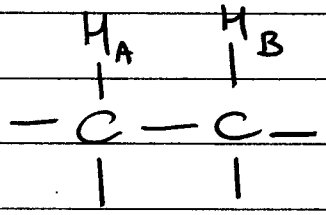
(1) $^1$H NMR

– A Index of Hydrogen Deficiency (READ)
(Degrees of Unsaturation)
(Double Bond Equivalents)

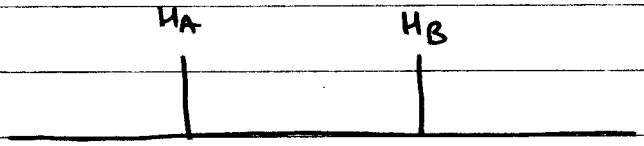
– SIGNAL SPLITTING

SPIN OF ONE NUCLEUS INFLUENCES THE CHEMICAL SHIFT OF A NEIGHBORING ONE

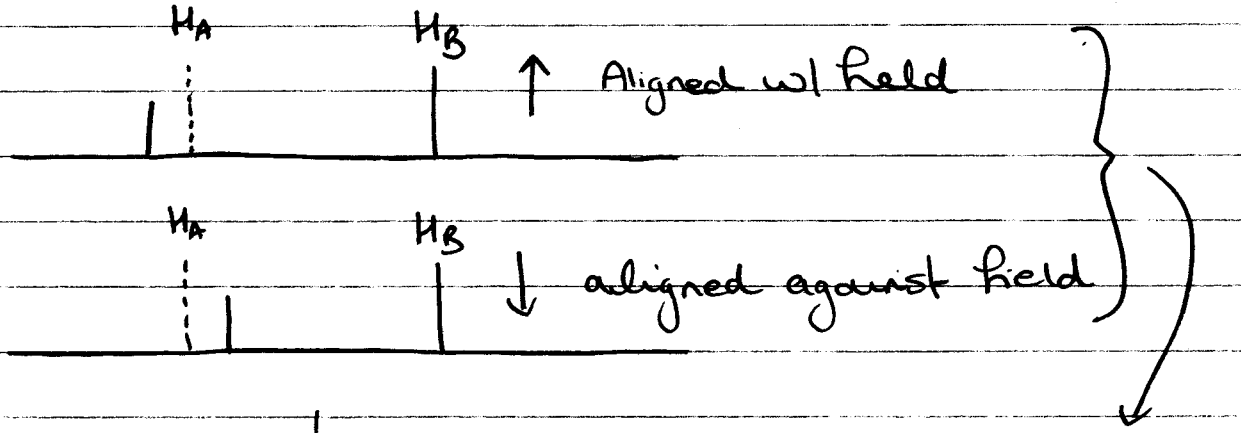
Consider two protons ⇓ Said to be COUPLED



With no interaction



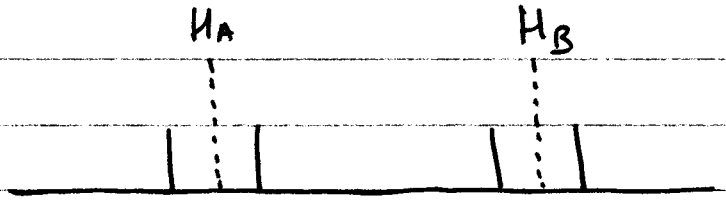

Consider spin of $H_B$



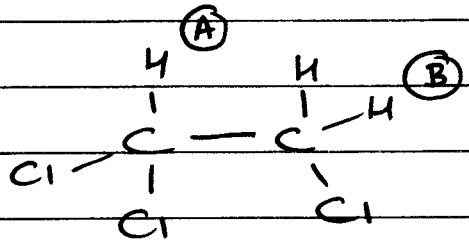

doublet

⇒ 2 peaks add up to intensity of original peak

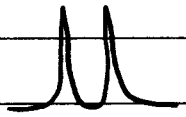
Coupling is reciprocal — if $H_B$ affects $H_A$, then $H_A$ must effect $H_B$



Consider:




consider signal for $H_B$

– $H_A$ can be ↑ or ↓ → 

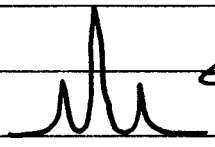
doublet

consider signal for $H_A$

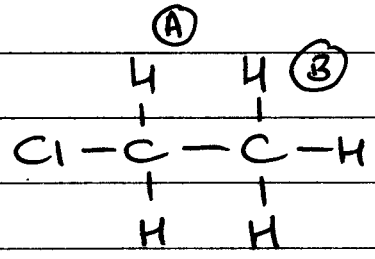
– $H_B$ can be ↑↑ —, ↑↓ ↓↑ —, ↓↓ — } 3 energy levels

↓

three peaks

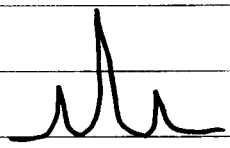
 ← triplet 1:2:1

consider



consider signal for $H_B$

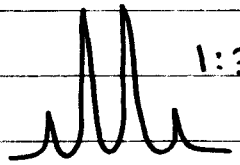
– $H_A$ can be ↑↑ / ↑↓ ↓↑ / ↓↓



1:2:1 triplet

consider signal for $H_A$

– $H_B$ can be ↑↑↑ / ↑↑↓ ↑↓↑ ↓↑↑ / ↑↓↓ ↓↑↓ ↓↓↑ / ↓↓↓



1:3:3:1

~~triplet~~ quartet

HOW DO WE FIGURE OUT WHAT THE INTENSITY RATIOS ARE –

NO MORE ARROWS !!

PASCALS triangle

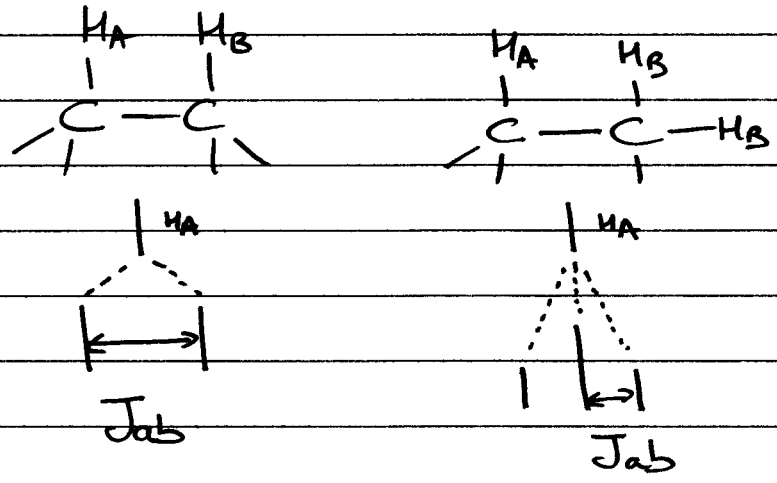
| | | | | | | # of neighbors | |
|---|---|---|---|---|---|---|---|
| | | | 1 | | | | singlet |
| | | 1 | | 1 | | 1 | doublet |
| | 1 | | 2 | | 1 | 2 | triplet |
| 1 | | 3 | | 3 | | 1 | 3 quartet |
| | 1 | | 4 | | 6 | 4 1 | 4 quintet |
| 1 | | 5 | | 10 | | 10 5 1 | 5 sextuplet |

# Coupling Constant (J)

Magnitude of Splitting

expressed in Hz (usually 0 - 18 with $^1H$)

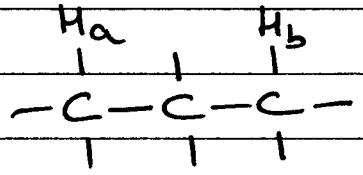
↳ independent of applied field




J values depend on:

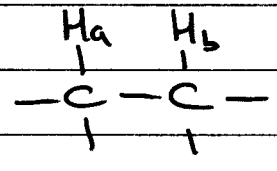
- BOND ANGLE
- BOND DISTANCE
- CHARACTERISTIC OF COMPOUND

IMPORTANT J values



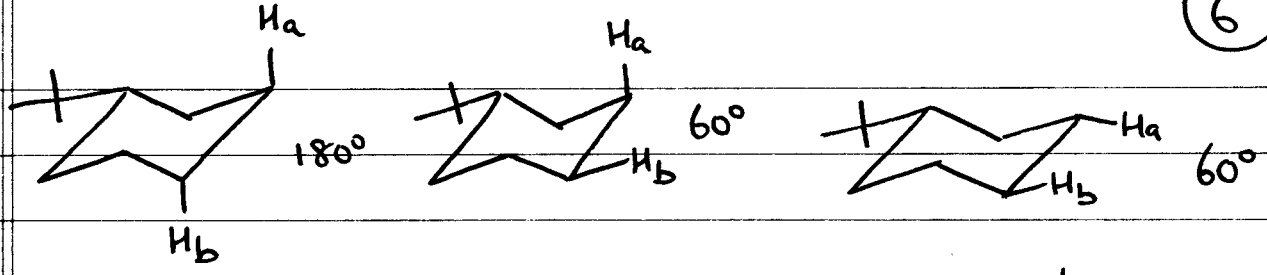

$J \ll 1$ Hz (IGNORE)

$^4J$ (4 BONDS)




Vicinal

$^3J = 6 - 8$ Hz

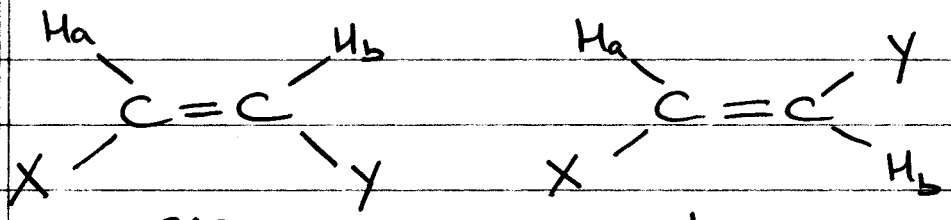



axial / axial
$J_{AB}$ = 8–14 Hz

axial / equatorial
$J_{AB}$ = 0–5 Hz

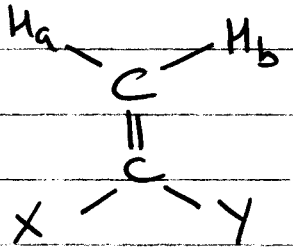
equatorial / equatorial
$J_{AB}$ = 0–5 Hz

## ALKENES

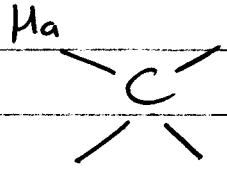



cis
5 – 10 Hz

trans
11 – 18 Hz

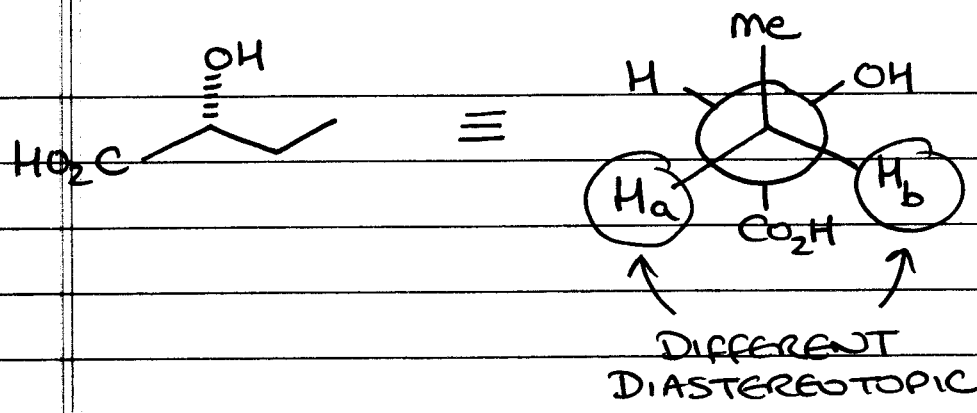



geminal $^2J$ = 0–5 Hz
(DIASTEREOTOPIC)




← DIASTEREOTOPIC

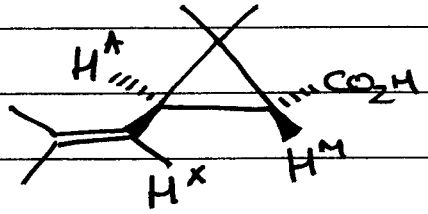
$^2J$ = 0–12 Hz
(very variable)

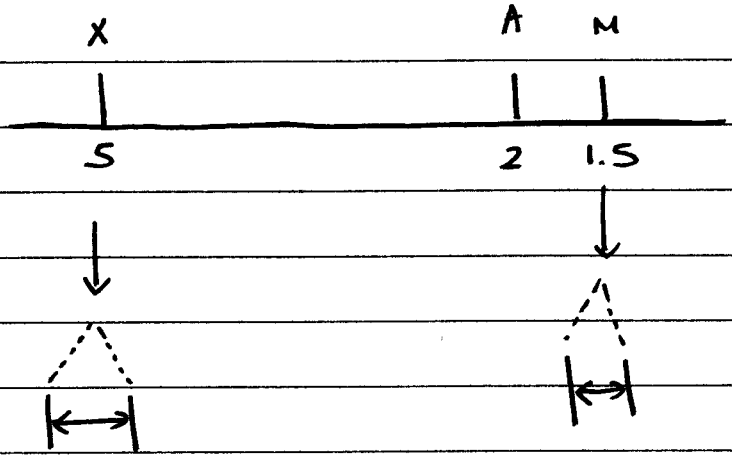



no matter how fast it rotates $H_a$ / $H_b$ always different

---

CHRYSANTHEMIC ACID




$J_{AX} = 8Hz$

doublet

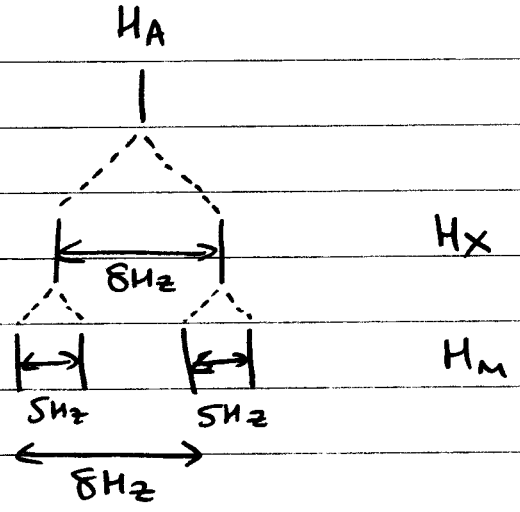
$J_{AM} = 5Hz$

doublet

Signal for $H_A$ is not a triplet

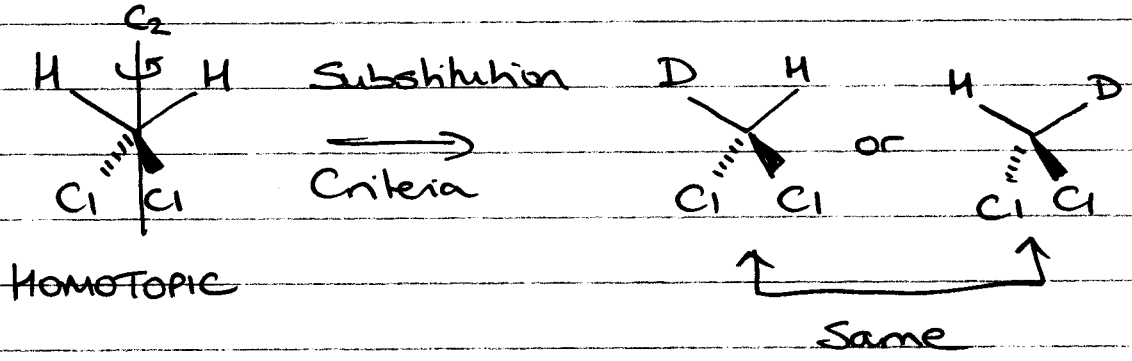
DOUBLET of DOUBLETS

→ splitting tree



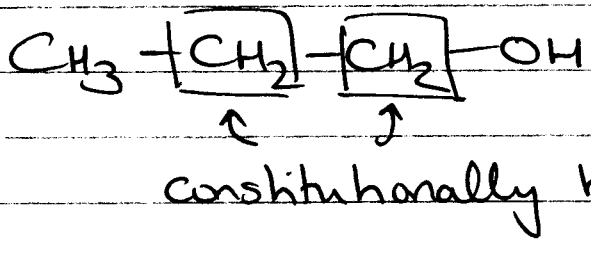

## SYMMETRY — TOPICITY

### HOMOTOPIC GROUPS
- can be exchanged by a $C_n$ axis




### HETEROTOPIC GROUPS
- ANY LIGANDS THAT ARE NOT HOMOTOPIC

(a) CONSTITUTIONALLY HETEROTOPIC



Stereoheterotopic

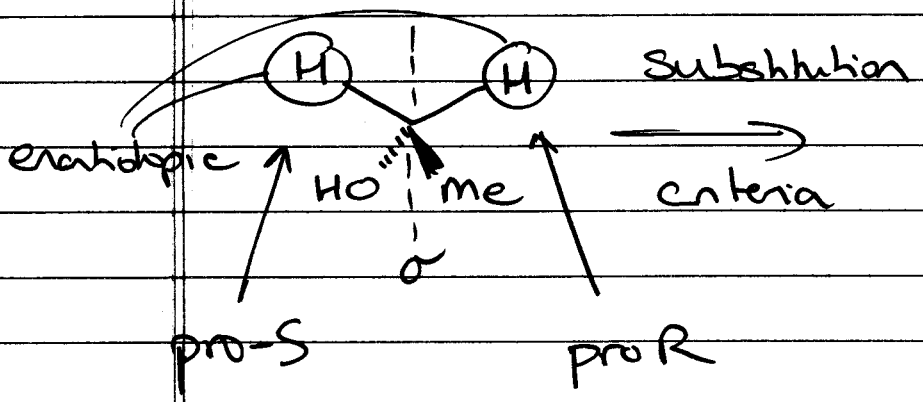
↳ enantiotopic or diastereotopic

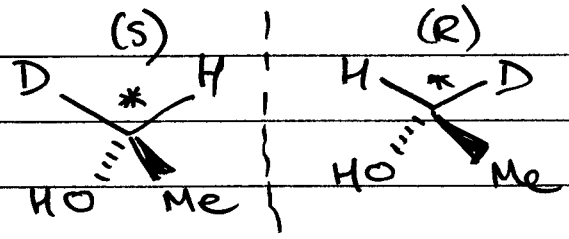
↓ can be exchanged by σ or i

↓ cannot be exchanged by any symmetry operation

ENANTIOTOPIC

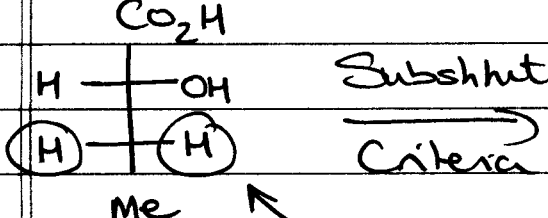
$MeCH_2OH$ ethanol



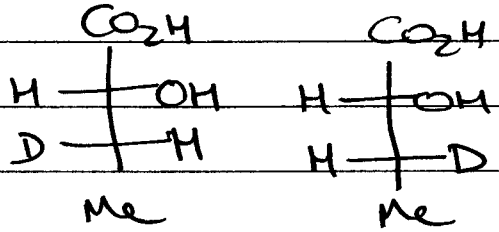

ENANTIOMERS

DIASTEREOTOPIC (FISCHER PROJECTIONS)

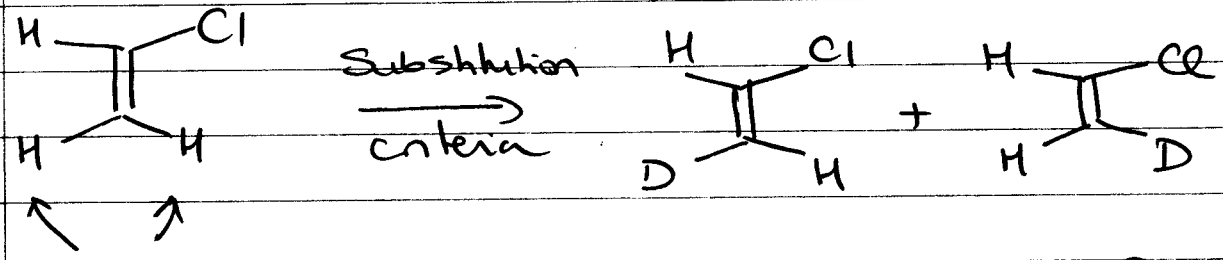



(R)-MALIC ACID

↖ Diastereotopic




DIASTEREOISOMERS




DIASTEREOTOPIC Hs

DIASTEREOISOMERS

| GROUP TOPICITY | CHEMICAL SHIFT |
|---|---|
| Homotopic | Identical |
| Enantiotopic | Identical |
| Diastereotopic | Different * |

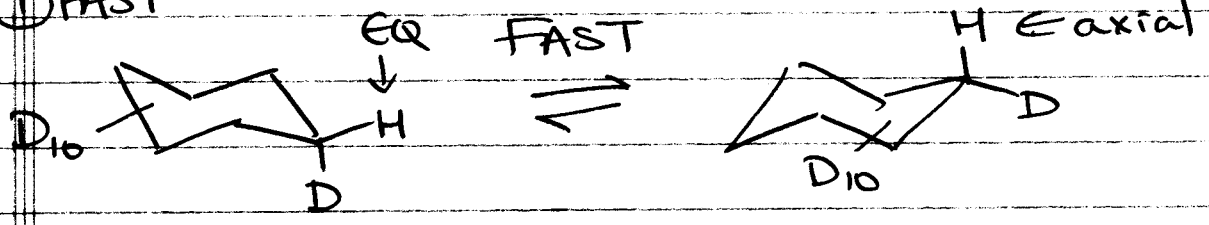
* Accidental chemical shift equivalency may occur.

---

DYNAMIC NMR

– remember methyl rotation

(1) FAST

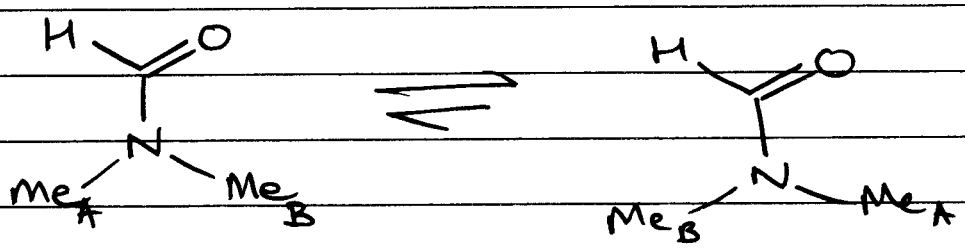



$^1H$ NMR at 25°C → one singlet

$^1H$ NMR at −100°C → two singlets

$\Delta G^{\ddagger} \sim 10$ kcal mol$^{-1}$

(2) SLOW

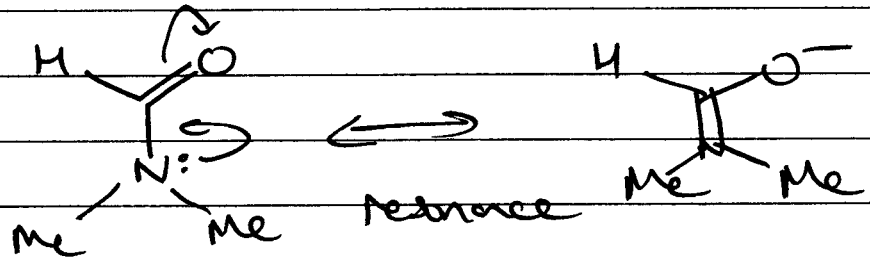



$^1H$ NMR at 28°C Two singlets

$^1H$ NMR at 120°C one singlet

$\Delta G^{\neq} \sim 17$ kcal mol$^{-1}$

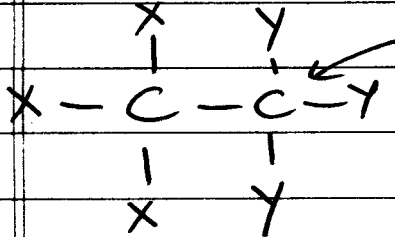
Reason:




Partial double bond character.

---

Back to $^{13}C$ NMR ⟶ why no coupling?

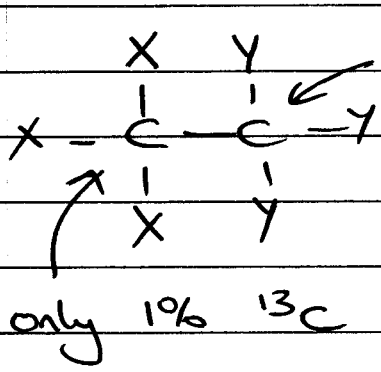



next to one C atom

⇒ doublet ?

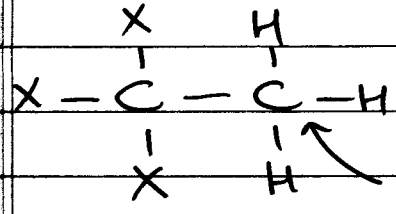
NO $^{13}C$ is ~1% abundant

$^{12}C$ is NMR silent




chances that two $^{13}C$ next to each other
1 in 10000 — just don't see it!

(↑ same reason why you don't see $^{13}C$ coupling in $^1H$ NMR spectra)

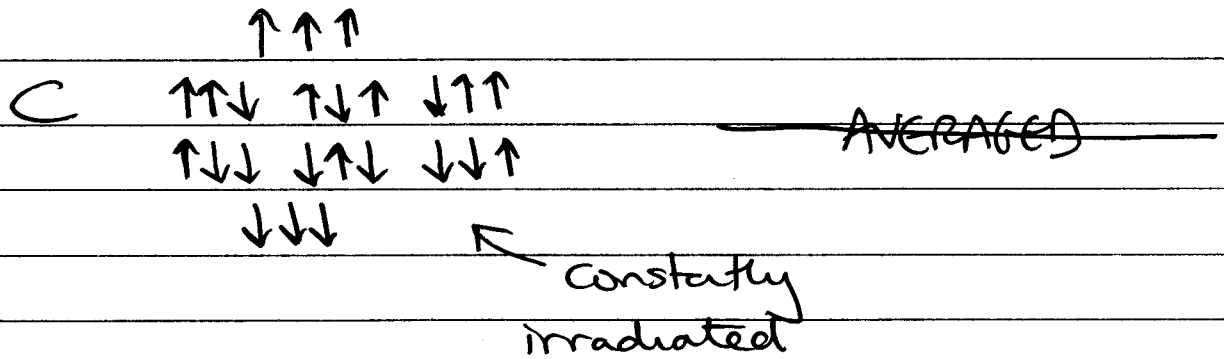



↓

quartet?

YES, but we decouple...

irradiate all probes continuously so C atom doesn't know what is up or down...



Lec (15) 

(1) HMK 13.6, 13.21–30
(2) Quiz on Wednesday
(3) CNSI Lecture
Tues 5pm CSSO
"Low Cost Nanometer Imaging Technology"
Grant Willson

---

(1) $^1$HNMR – splitting cont
(2) Double Bond Equivalents (DBE)

---

(2) Double Bond Equivalents

- can do it by drawing any structure w/ correct formula

e.g. $C_4H_7NO$

← 2 double bonds
= 2 DBE

| | | |
|---|---|---|
| 1 double bond | = | 1 DBE |
| 1 ring | = | 1 DBE |
| 1 alkyne | = | 2 DBE |
| 1 aromatic (benzene) ring | = | 4 DBE (3 C=C's, 1 ring) |

No N atoms just C, H, O

n Carbon atoms

maximum possible H atoms = $(2n+2)$

Subtract actual # of H atoms, divide number by 2 to get DBEs

e.g.  2 DBEs

$n = 7$, $2n+2 = 16$

actual H atoms = 12

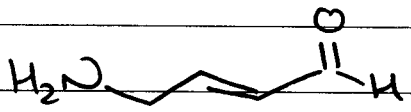
$$\frac{16-12}{2} = 2 \text{ DBEs}$$

With N atoms

n C atoms, max H = $2n+2$,

Subtract actual H atoms, then add 1 for each nitrogen, then divide by 2

e.g.



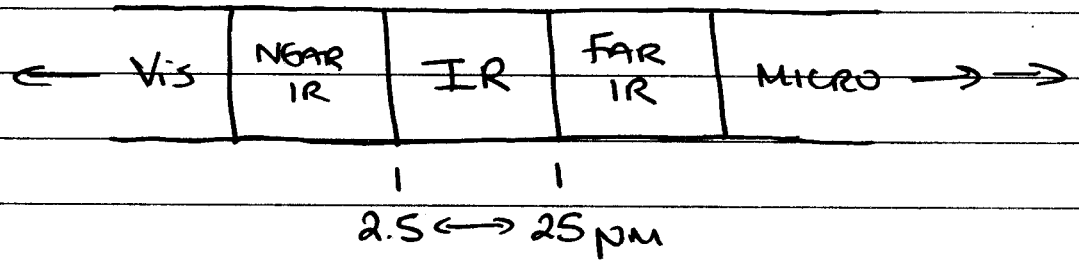
$C_4H_2NO$

$2n+2 = 10 - 7 = 3 + 1 = 4/2 = 2$

If you have other atoms in structure — best to draw a test structure

For each halogen, just pretend it is a H atom.

# IR Spectra

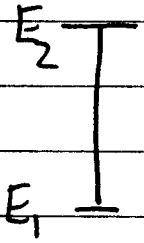



Corresponds to

4000 → 400 $cm^{-1}$

wavenumber = waves per centimeter

$cm^{-1}$ = "reciprocal centimeters"

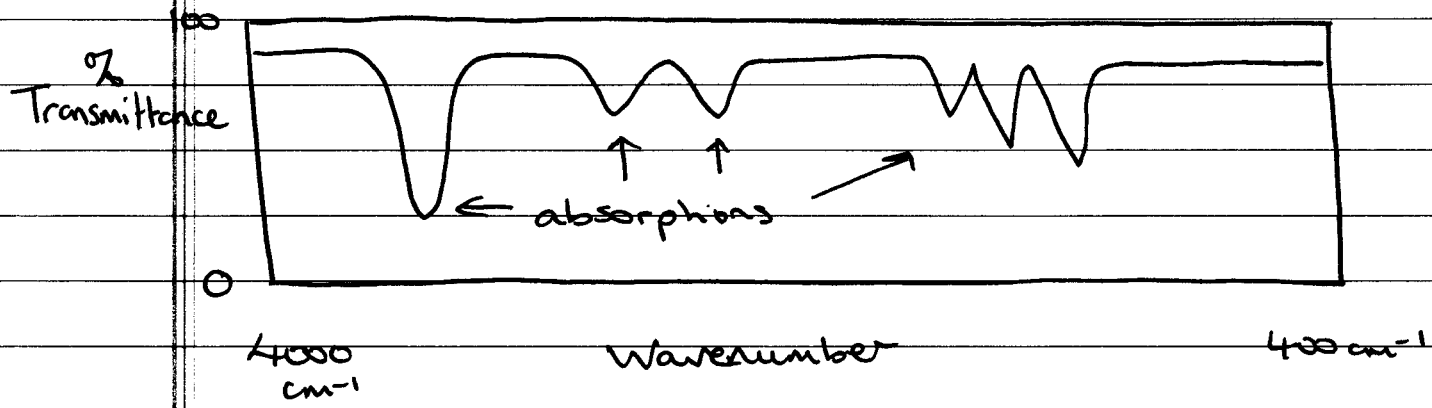



$\Delta E$ = 2 - 10 kcal $mol^{-1}$

⇒ MOLECULAR VIBRATIONS

## What the IR Spectrum looks like






## REGIONS (4 DISTINCT ONES)

| | | | |
|---|---|---|---|
| N-H<br>O-H<br>C-H | C≡N<br>C≡C | C=O<br>C=N<br>C=C | single bonds |

4000 — 2500 — 2000 — 1500

- bonds to HYDROGEN
- triple bonds
- double bonds
- FINGERPRINT REGION

GOOD WAY TO IDENTIFY FUNCTIONAL GROUPS

+ ANY VIBRATION THAT CAUSES A CHANGE IN DIPOLE MOMENT IS IR ACTIVE

- more polar bonds => stronger absorption

IR spectra are complicated (UGLY)

Lec (17) 

(1) HMK 12.1 — 12.12
(2) Quiz 2
low 3, HIGH 32, AVERAGE 19

---

(1) IR continued

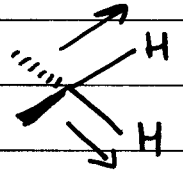
---

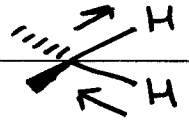
NON-LINEAR MOLECULE w/ N atoms

3N-6 fundamental vibrations

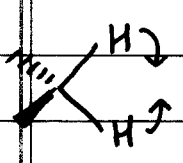
STRETCHING

SYMMETRIC ↙ ↘ ASYMMETRIC

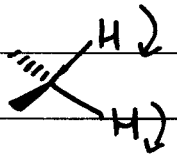


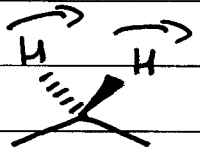

BENDING



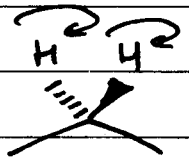

SCISSORING




ROCKING




WAGGING




TWISTING...

Bending requires less energy than stretching

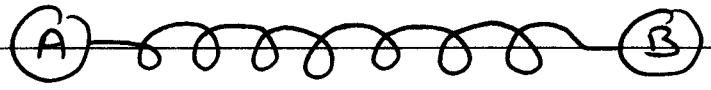
(Iron bar analogy)

↳ bending at lower wavenumbers (lower energy) than stretching.

---

CONCENTRATE ON STRETCHING

↳ use a simple model




→ treat as a harmonic oscillator
- derived from Hooke's law

$$\nu = \frac{1}{2\pi c}\sqrt{\frac{k}{N}}$$

$\nu$: frequency

$k$: force constant

$N$: reduced mass

or

$$\bar{\nu} = 4.12\sqrt{\frac{k}{N}}$$

$\bar{\nu}$: wavenumber ($cm^{-1}$)

$k$: force constant in dynes

$N$: reduced mass $\frac{m_A m_B}{m_A + m_B}$

$m_A/m_B$ mass of atoms in atomic units

What does this mean?

Lighter atoms ⟹ higher freq vibration

| C–H | C–D | C–O | C–Cl |
|---|---|---|---|
| ~3000 cm$^{-1}$ | ~2200 cm$^{-1}$ | ~1100 cm$^{-1}$ | 700 cm$^{-1}$ |

Stronger bonds ⟹ higher freq vibration

| C≡C | C=C | C–C |
|---|---|---|
| ~2100 cm$^{-1}$ | ~1600 cm$^{-1}$ | ~1100 cm$^{-1}$ |

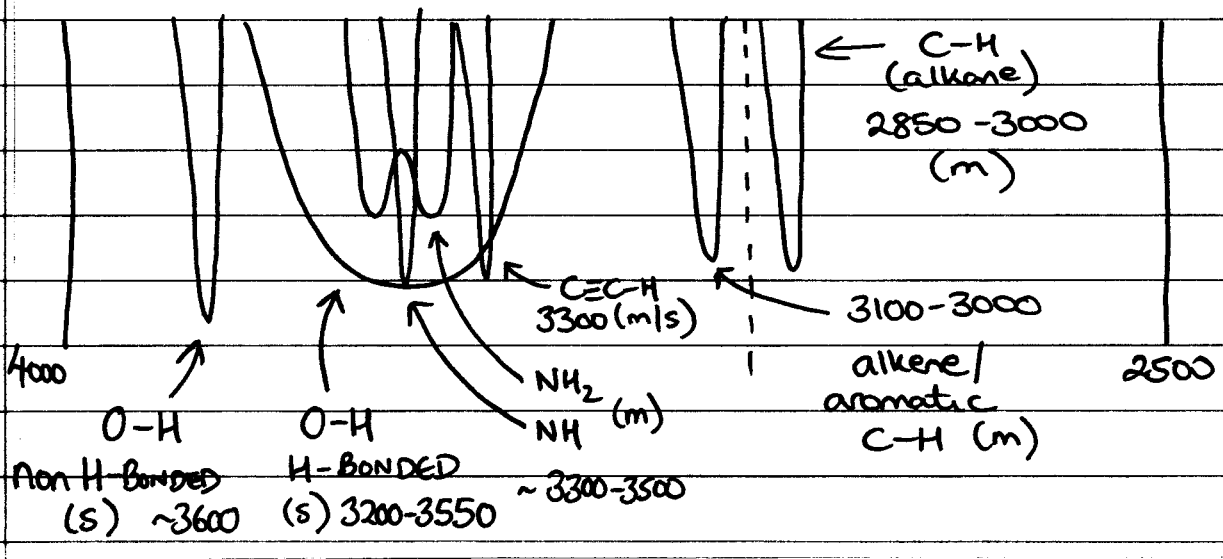
<u>ALSO</u>

Intensity of Signal INCREASES as bond polarity increases O–H > N–H > C–H

ALL COMES DOWN TO TABLES...

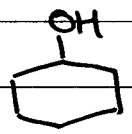
BUT REGIONS

4000 – 2500 cm$^{-1}$ BONDS TO H



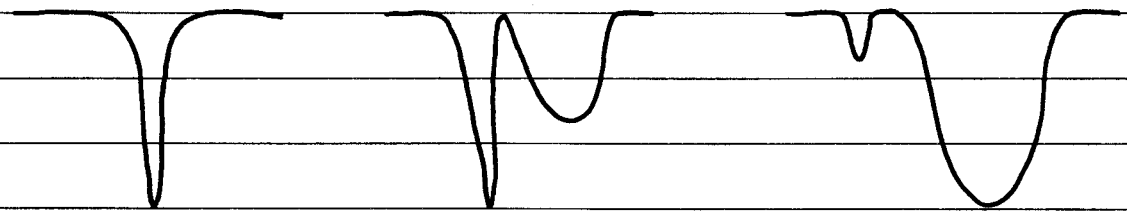
# H- BONDING EFFECTS

↳ shift to lower wavenumber




in $CCl_4$

0.01 M 0.1 M 1 M



Less H-Bonding at higher dilution

---

2500 - 2000 $cm^{-1}$ (TRIPLE BONDS)

| | | |
|---|---|---|
| C≡C | 2100 - 2250 $cm^{-1}$ | (weak) |
| C≡N | ~2250 | (strong) |

---

2000 - 1500 $cm^{-1}$ (DOUBLE BOND REGION)

3 IMPORTANT ONES

C=O intense → see later (~1600 - 1800)

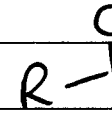
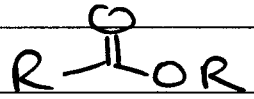
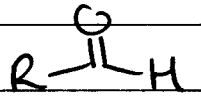
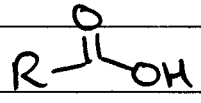
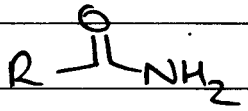
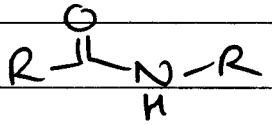
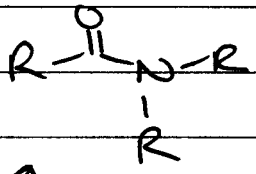
C=C 1600 - ~1680 $cm^{-1}$ w/m

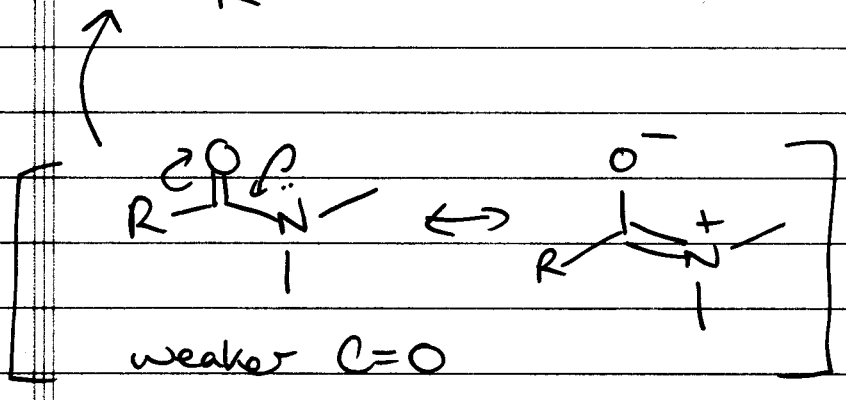
Aromatic C=C 1450 - 1600 $cm^{-1}$ (weak)

$NO_2$ 1 at ~1550, 1 at ~1350 (strong)

# STRONGER C=O



| $cm^{-1}$ | | | EXTRAS |
|---|---|---|---|
| ~1800 |  | acid chloride | |
| ~1750 |  | ester | C–O stretch 1300 – 1000 $cm^{-1}$ |
| ~1730 |  | aldehyde | 2 weak C–H stretch 2850 & 2750 |
| ~1720 |  | ketone | |
| ~1710 |  | carboxylic acid | O–H stretch ~ 2500 – 3300 |
| ~1710 |  | 1° amide | 2 N–H stretches at ~3400 |
| ~1690 |  | 2° amide | 1 N–H stretch at ~3400 |
| ~1670 |  | 3° amide | no N–H stretch at 3400 |



weaker C=O

Less than 1500 $cm^{-1}$

single bonds C–C, C–O etc

⇒ FINGERPRINT REGION

C–O only really useful indicator

1000 – 1250 $cm^{-1}$ (strong)

C–H bonds come in here too

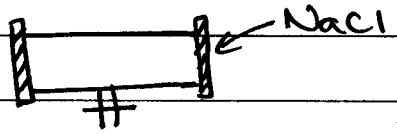
$CH_2$ ~1450 $cm^{-1}$ (m)

$CH_3$ ~1375 / 1450 $cm^{-1}$ (w/m)

---

SAMPLE PRACTICALITIES

(a) GASES – cell




(b) LIQUIDS – neat between NaCl plates

(c) SOLIDS – MULLS (in paraffin)
KBr pellet

---

READ sect 12.5

Lec (17) ?



(1) CNSI Lecture
"Protein Design: Theory, Experiments, and Applications in the Bionanosciences"
Homme Hellinga – Duke.

Ch 14 PROBLEMS

---

(1) MASS SPECTROMETRY

- not spectroscopy
(nothing to do with transitions between energy levels)

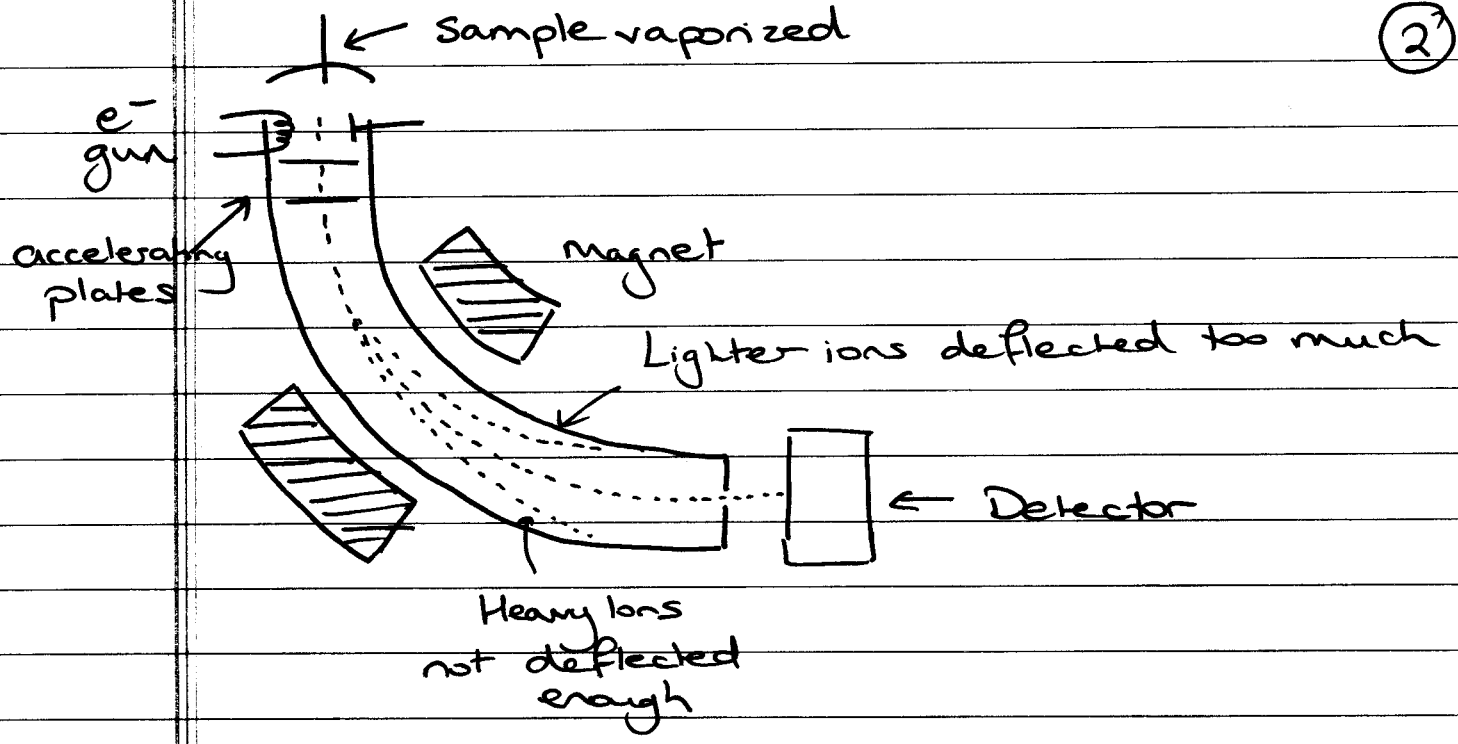
- measures molecular weight

⇓

molecular formula

HOW DO WE DO THIS

(1) Vaporize molecule HEAT/VACUUM
(2) Ionize sample (High energy electrons)
(3) Accelerate Ions (Charged Plates)
(4) Pass through magnetic field (Ion sorting)
(5) Detect Ions




Vary accelerating voltage or magnetic field
→ sorts ions by mass / charge ratio

Assume charge on ions is +1 → effectively sorting by mass

$$\frac{m}{z} = \frac{m}{1} \equiv \text{mass of ion}$$

~~~

IONIZATION

- High energy electrons ~ 70 eV
  (1 eV = 23 kcal mol$^{-1}$)

potential
Ionization of most organic molecules 8-15 eV
~~~

$$M + e^- \longrightarrow M^{+\bullet} + 2e^-$$

molecule → molecular ion (radical cation)

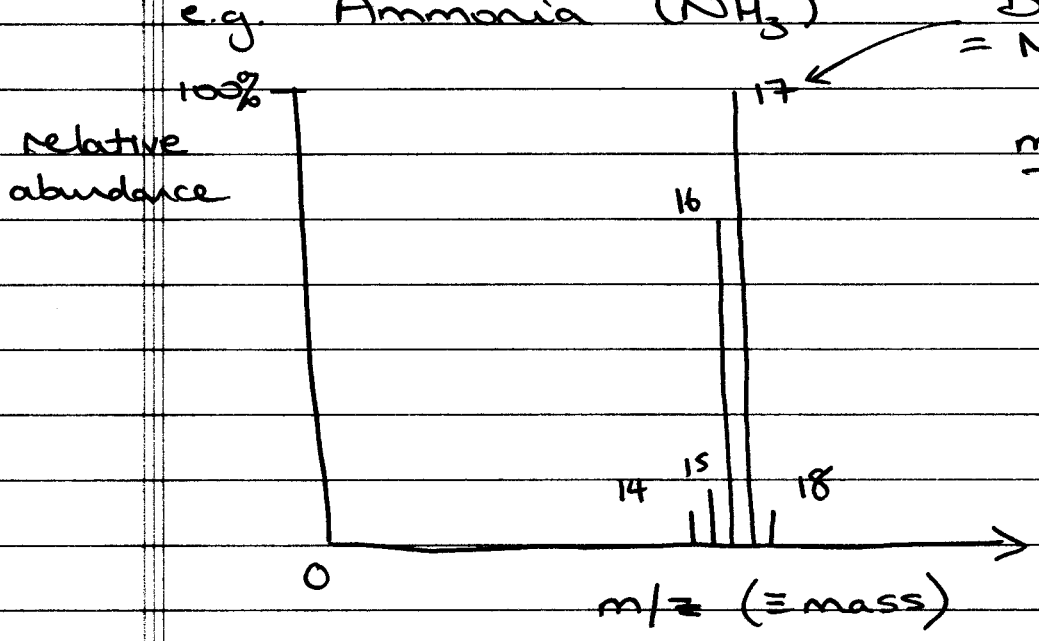
Fate of $M^{+\bullet}$ → detected

↓ fragmented

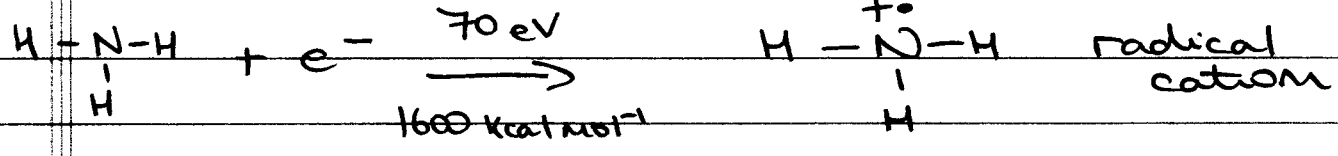
$\underline{\underline{A^+}} + B^\bullet$ or $A^\bullet + \underline{\underline{B^+}}$

Lot of excess energy → molecular ions just fly apart.

e.g. Ammonia ($NH_3$)




| m/z | Rel. ab. |
|---|---|
| 14 | 2.2 |
| 15 | 7.5 |
| 16 | 80 |
| 17 | 100 |
| 18 | 0.4 |




Surplus energy causes (50–100 kcal mol⁻¹ to break bond)

$NH_3 \xrightarrow{(-e^-)} {}^{+\bullet}NH_3 \xrightarrow{(-H^\bullet)} H\text{-}\overset{\overset{\cdot\cdot}{|}}{\underset{|}{N}}\text{-}H \xrightarrow{(-H^\bullet)} H\text{-}N: \xrightarrow{(-H^\bullet)} :N:$

m/z: 17 → 16 → 15 → 14

Breaking N–H bonds

What about small peak at m/z = 18

## ISOTOPES

| | common | other |
|---|---|---|
| hydrogen | $^1H$ (100) | $^2H$ (0.016) |
| nitrogen | $^{14}N$ (100) | $^{15}N$ (0.38) |

So m/z = 18 for $^{15}N^1H_3$ or $^{14}N^1H_2{}^2H$

mainly this one

$^{15}N$ more common than $^2D$

## COMMON ISOTOPES

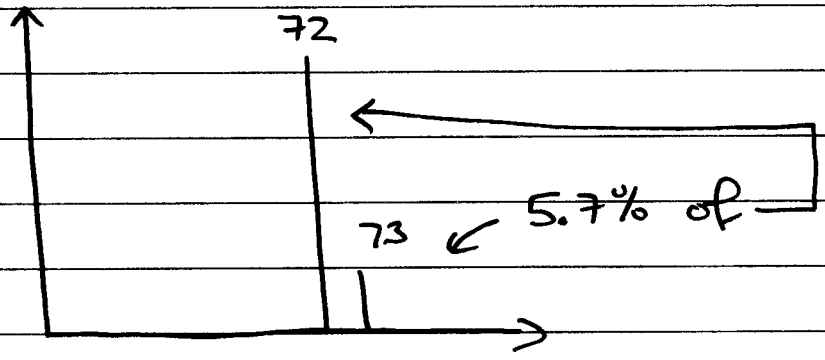
| | | M+1 | M+2 |
|---|---|---|---|
| Hydrogen | $^1H$ (100) | 0.016 | — |
| Carbon | $^{12}C$ (100) | 1.11 | — |
| Nitrogen | $^{14}C$ (100) | 0.38 | — |
| Oxygen | $^{16}O$ (100) | 0.04 | 0.2 |
| Sulfur | $^{32}S$ (100) | 0.78 | 4.4 |
| Chlorine | $^{35}Cl$ (100) | — | 32.5 |
| Bromine | $^{79}Br$ (100) | — | 98 |

## (M+1) PEAKS

↳ good way to determine # of C atoms in a molecule. $^{13}C$ is major contributor to M+1 peak, –

Set $M^+$ to 100%
– calculate intensity of M+1 Peak

e.g. $C_5H_{12}$




$$M+1\ \% = \underset{\#C\text{ atoms}}{(5 \times 1.1)} + \underset{\#H\text{ atoms}}{(12 \times 0.016)}$$

$$= 5.5 + 0.2 \text{ small.}$$

$$= 5.7$$

So, divide $\frac{5.7}{1.1} \approx 5$ C ATOMS

## (M+2) PEAKS

Significant for S, Cl, Br

$^{32}S/^{34}S \sim 19:1$
$^{35}Cl/^{37}Cl \sim 3:1$
$^{79}Br/^{81}Br \sim 1:1$
} very diagnostic for the presence of one of these elements

If M+2 peak < 1%, then none of these elements are present

---

Other useful rules

$M^{+\bullet}$ ODD or EVEN

# of N atoms is ODD
1, 3, 5...

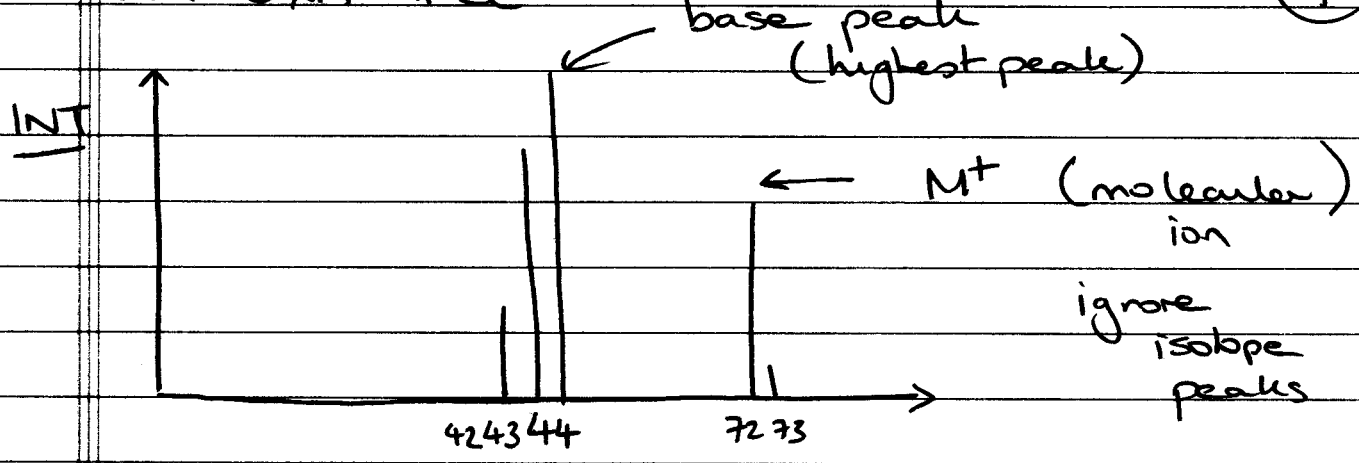
# of N atoms is EVEN
0, 2, 4, ...

$C_nH_{2n+2}$ rule

Most number of H atoms a molecule w/ n C atoms = $2n+2$

---

# An Example




$M^+$ = even, no N or 2 N

$M^+ + 1$ peak = 4.8% of $M^+$

$\frac{4.8}{1.1} \approx 4$ C atoms

$C_4 = 48$

$72 - 48 = 24 \Rightarrow C_4H_{24}$ IMPOSSIBLE

max $H = 2n + 2 = 10$,

So, what about 1 x Oxygen

$24 - 16 = 8$, hence $C_4H_8O$

↑
reasonable formula

# LOW vs HIGH RESOLUTION



- LOW (everything so far) ⇒ NOMINAL MASS
- HIGH ⇒ precise mass → based on $^{12}C = 12.0000$ (defn)

consider $C_3H_6O$ 58 } Low res good enough
$C_3H_8O$ 60 }

consider $C_3H_8O$ 60 } Low res will not distinguish
$C_2H_4O_2$ 60 }

HIGH RES $C_3H_8O$ 60.0575 ← High res will distinguish
$C_2H_4O_2$ 60.0211

± 0.0001 AMU ↓

So accurate, will also give you a molecular formula.

e.g.
$O_2$ (32) 31.9898
$N_2H_4$ (32) 32.0375
$CH_3OH$ (32) 32.0262

# FRAGMENTATION

- Cation Stabilities

$CH_3^+ < 1^{o+} < 2^{o+} < 3^{o+} <$ ALLYLIC/BENZYLIC

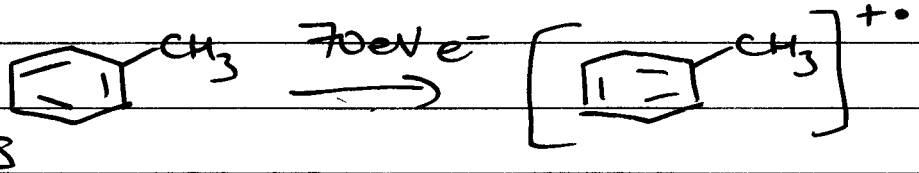
(Resonance Effects)

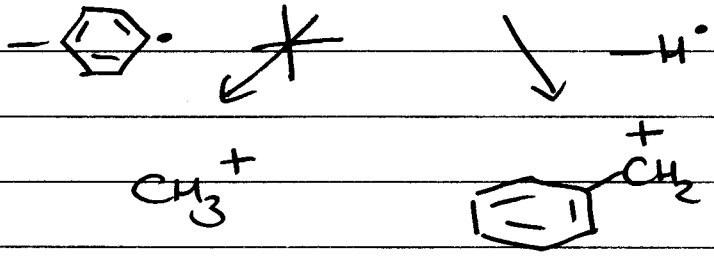
- Rearrangements

$\Longrightarrow$ MESS $\Longrightarrow$ FINGERPRINT (like IR) → Match to database

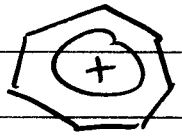
---

SOME GUIDELINES



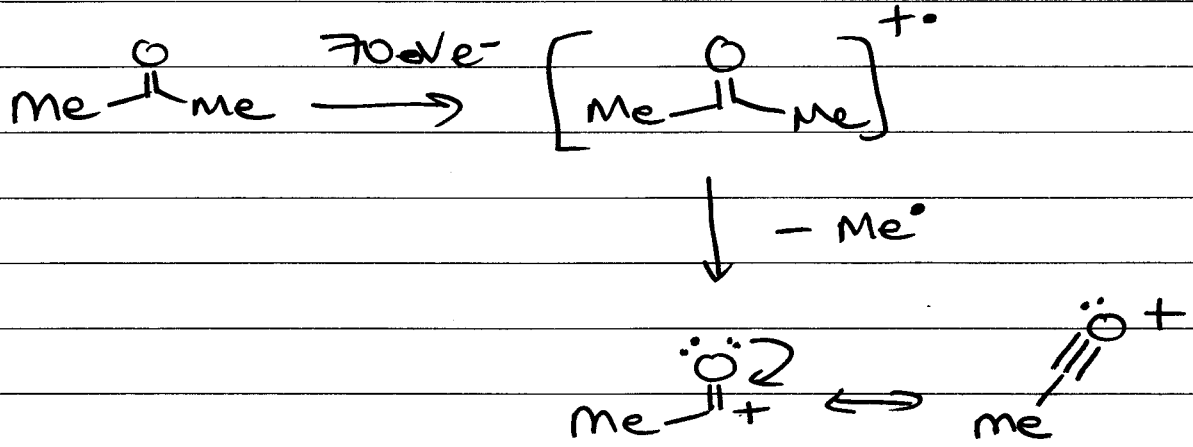




Benzylic 91



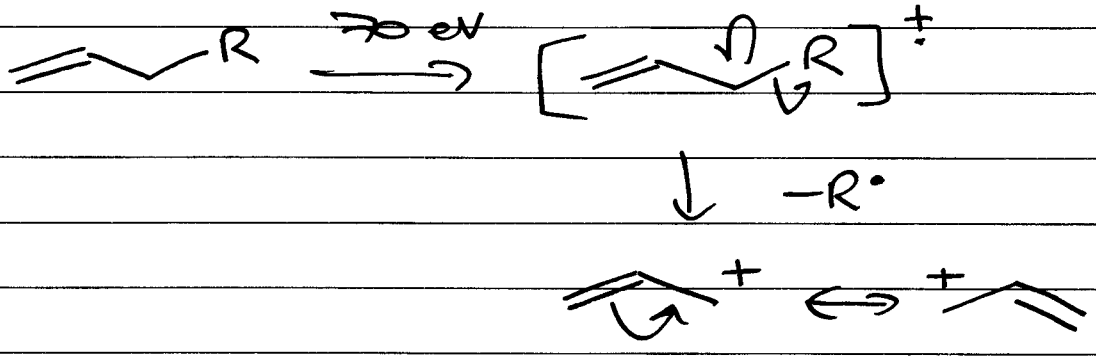
Tropylium (aromatic)

## ACYLIUM IONS

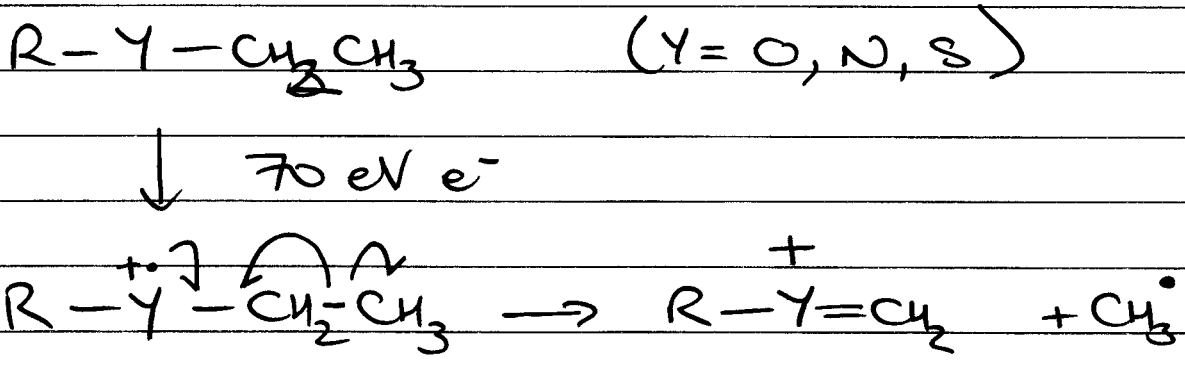



Carbonyl compounds show intense fragments from acylium ions.

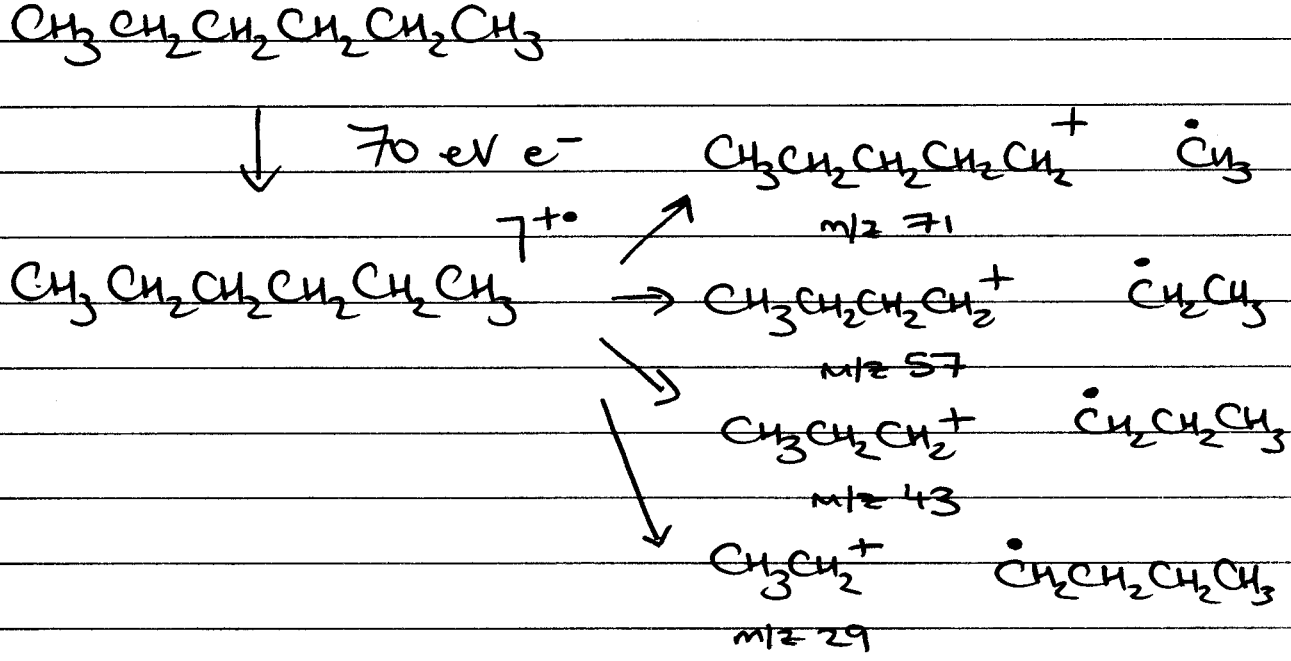
## ALKENES → ALLYLIC CATIONS




## HETEROATOMS



HEXANE



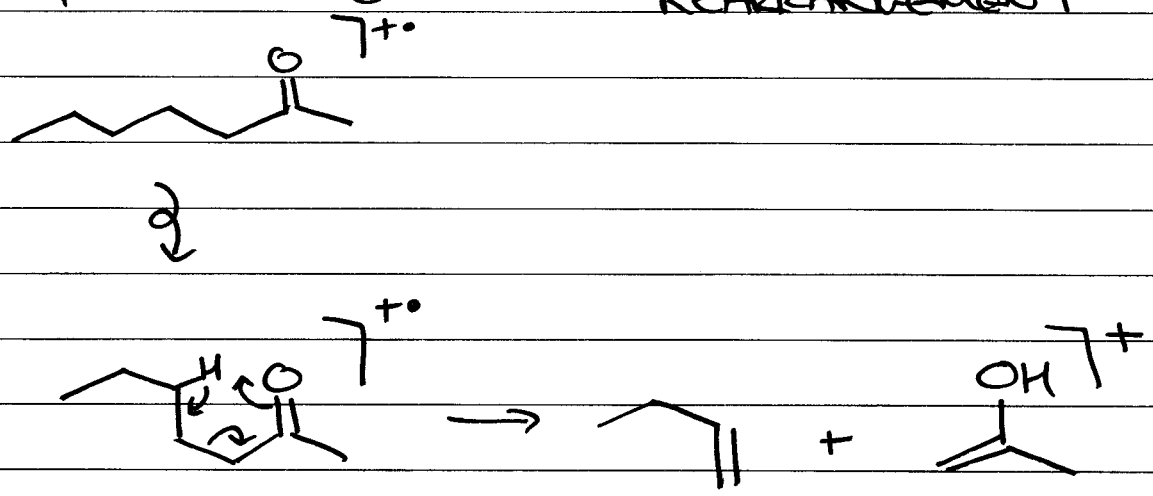

* MCLAFFERTY

SOFT-IONIZATION TECHNIQUES

CI — Chemical Ionization
FABMS — Fast Atom Bombardment MS
MALDI-MS — Matrix Assisted Laser Desorption Ionization MS
ES-MS — Electrospray MS

softer ionization, much less fragmentation, easier to see $M^+$ (molecular ion peak)

C=O also give McLAFFERTY REARRANGEMENT



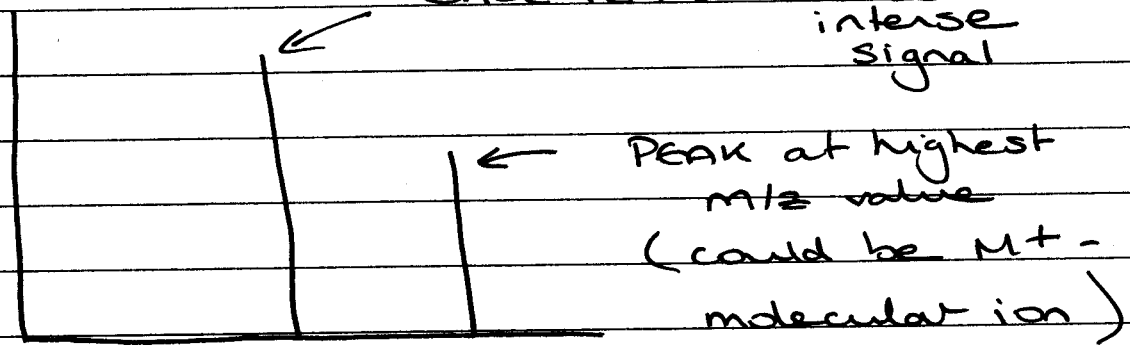
LEC (18)



HMK 16.4, 16.5, 16.19–16.29

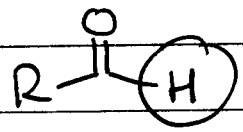
(1) MASS SPEC cont...
(2) CARBONYL CHEM.

(1)

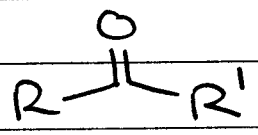



(2) CARBONYL CHEMISTRY

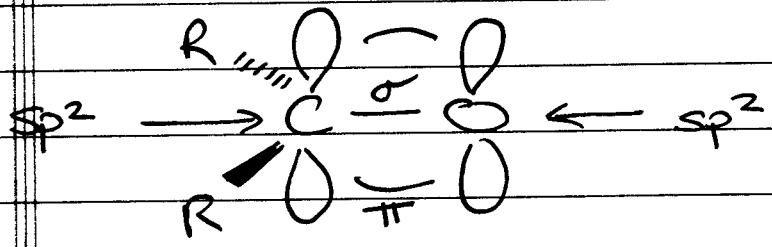
ALDEHYDES

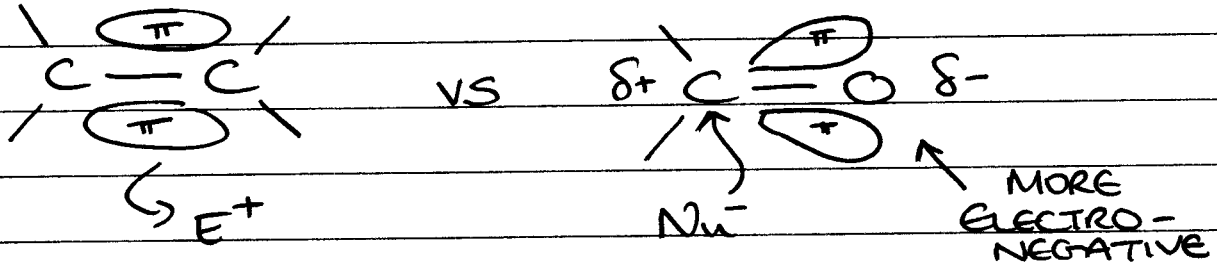


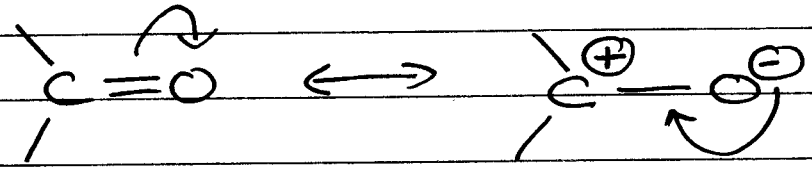

KETONES



C=O group



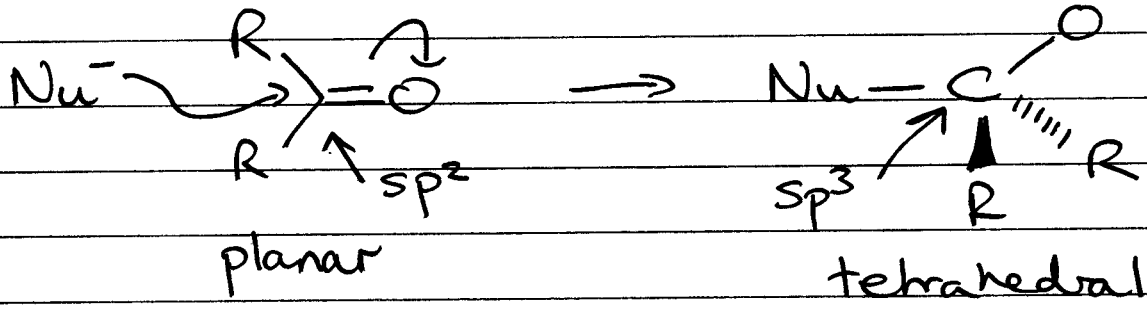




more important resonance contributer

---

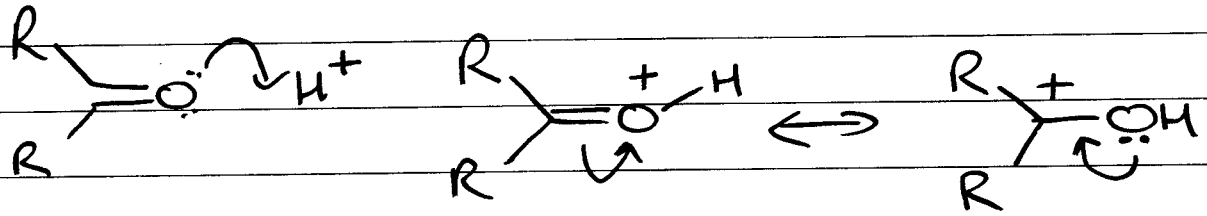
REACTIONS: Nucleophilic addition

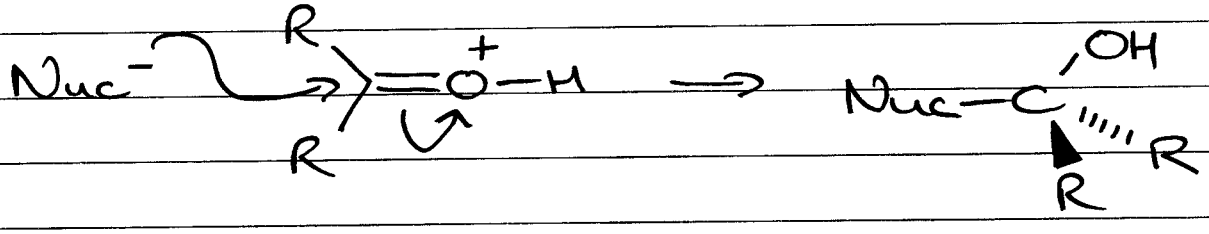



planar

tetrahedral

Activation with $H^+$ or Lewis Acid

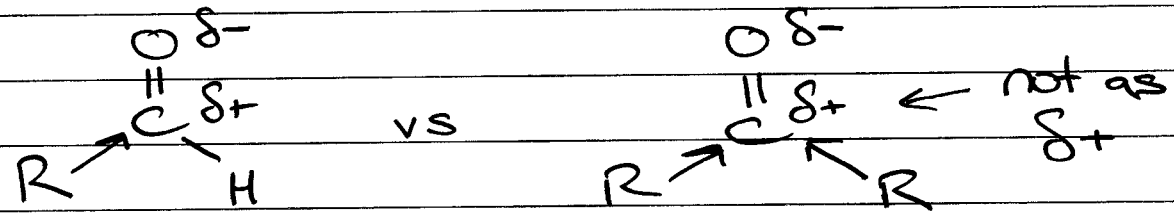




Aldehydes more reactive than ketones

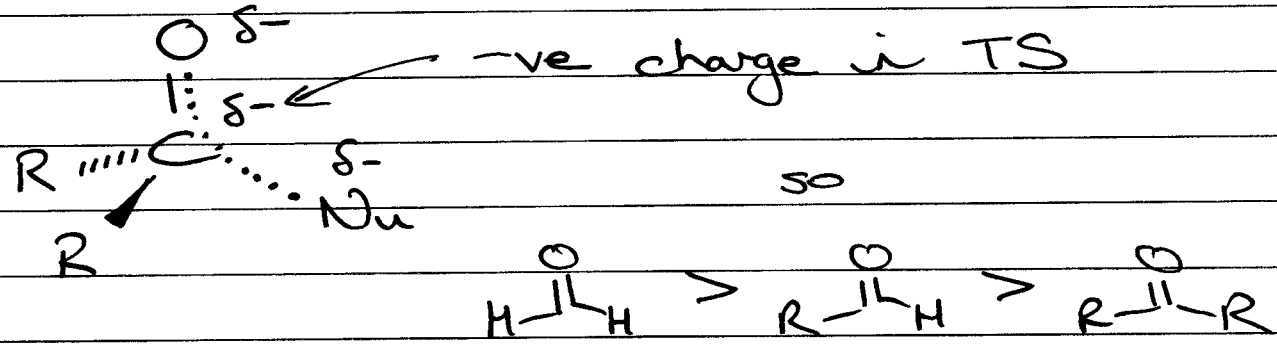
(1) Less bulky 1 R vs 2 R

(2)



R → inductive effect

(3) TS of reaction



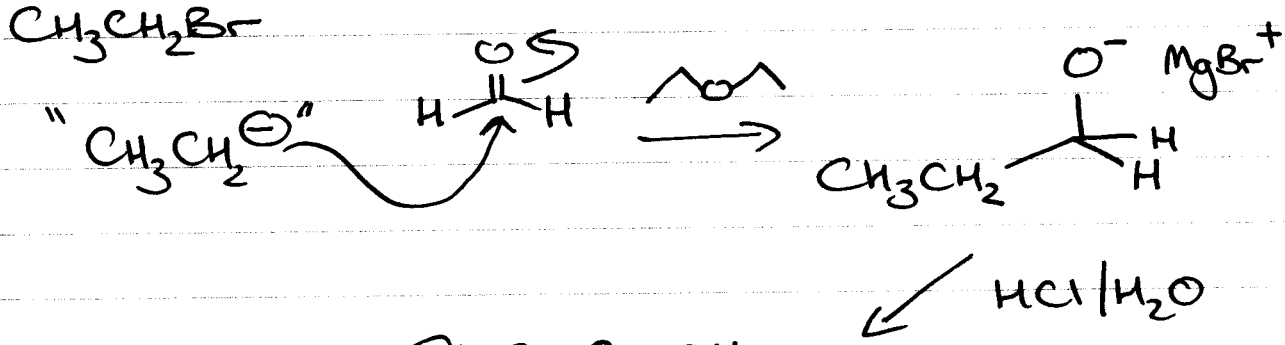
# CARBON NUCLEOPHILES

$RMgX$ $RLi$ $RC\equiv C^{\ominus}$ $^{\ominus}CN$

Important C–C Bond formation

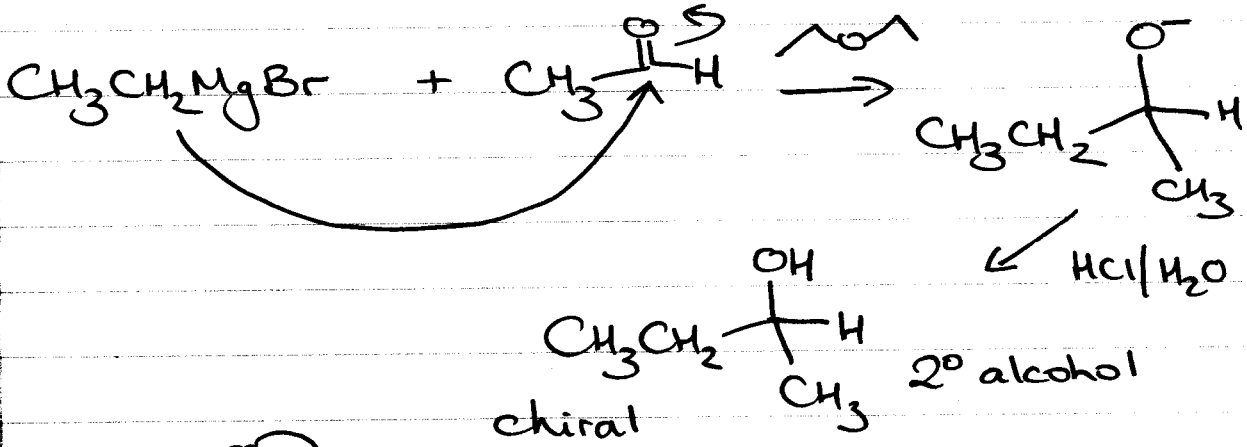
## (1) GRIGNARDS

### (i) FORMALDEHYDE

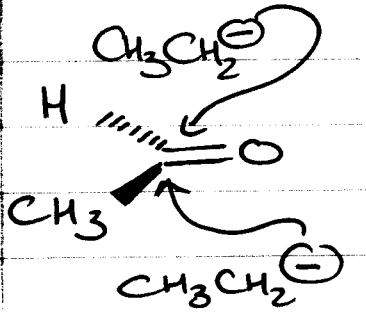



$CH_3CH_2CH_2OH$
1° alcohol

### (ii) ALDEHYDE not H–CHO

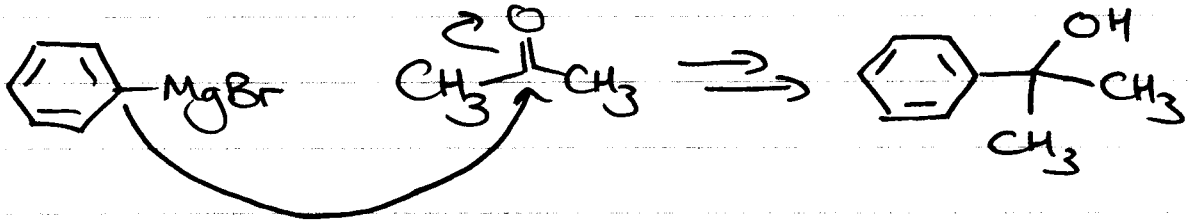



chiral — 2° alcohol

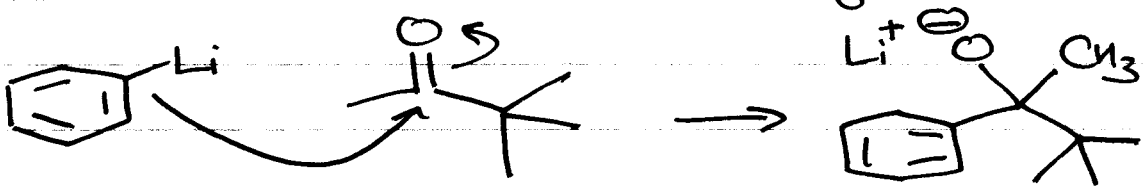



→ ENANTIOMERS (draw them)

(iii) KETONES

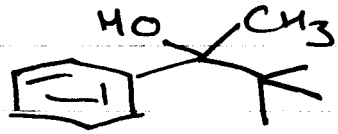



(2) ORGANOLITHIUMS (more reactive than Grignards)

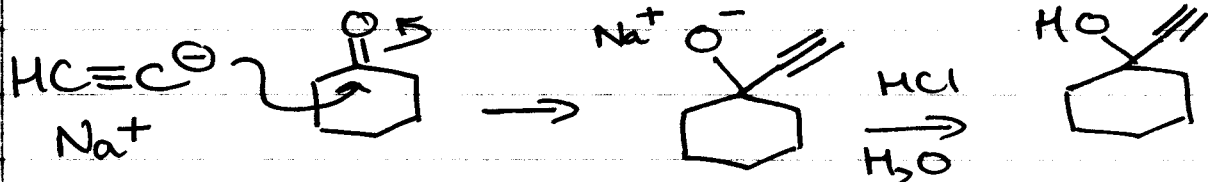


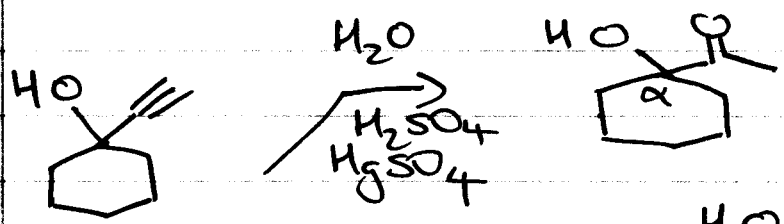

STERICALLY HINDERED

↓ HCl/H2O

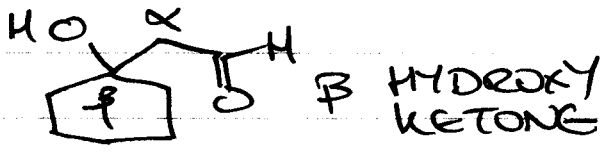



(3) ALKYNYL ANIONS R–C≡C⊖



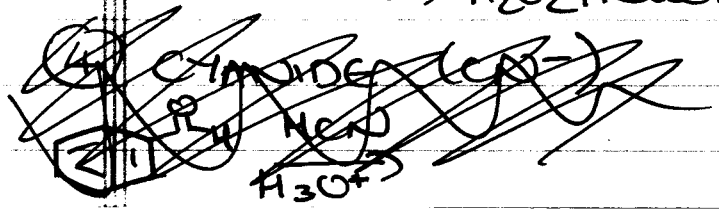




α HYDROXY KETONE




β HYDROXY KETONE

(i) (sia)2BH
(ii) H2O2/NaOH



Lec (19) 

(1) HMK 16.17 – 16.18, 16.30 – 16.39

(2) MIDTERM nxt WEDS
- problems handout Monday in class

---

(1) CARBON Nucleophiles
(2) OXYGEN Nucleophiles

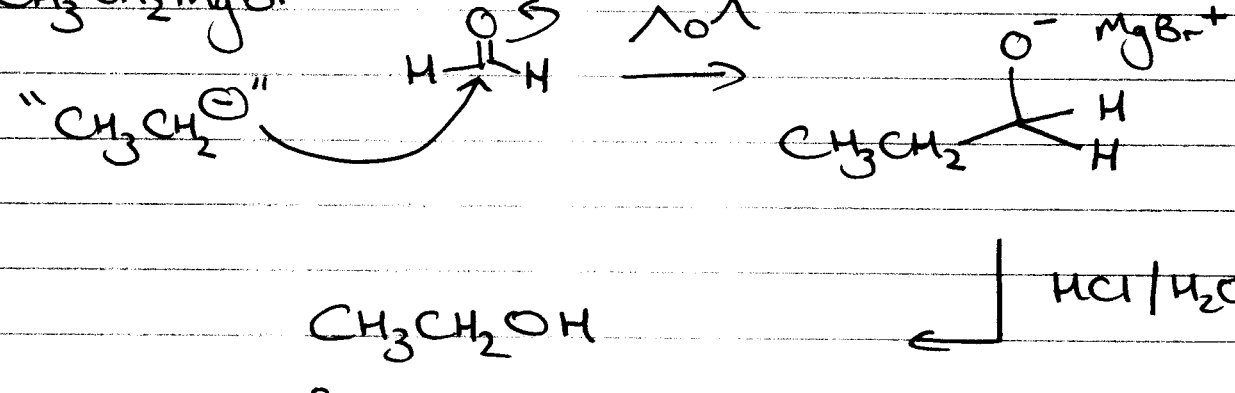
---

(1) $RMgX$ $RLi$ $RC{\equiv}C^{\ominus}$ $^{\ominus}CN$

Important for C–C Bond formation

(A) Grignards $RMgX$

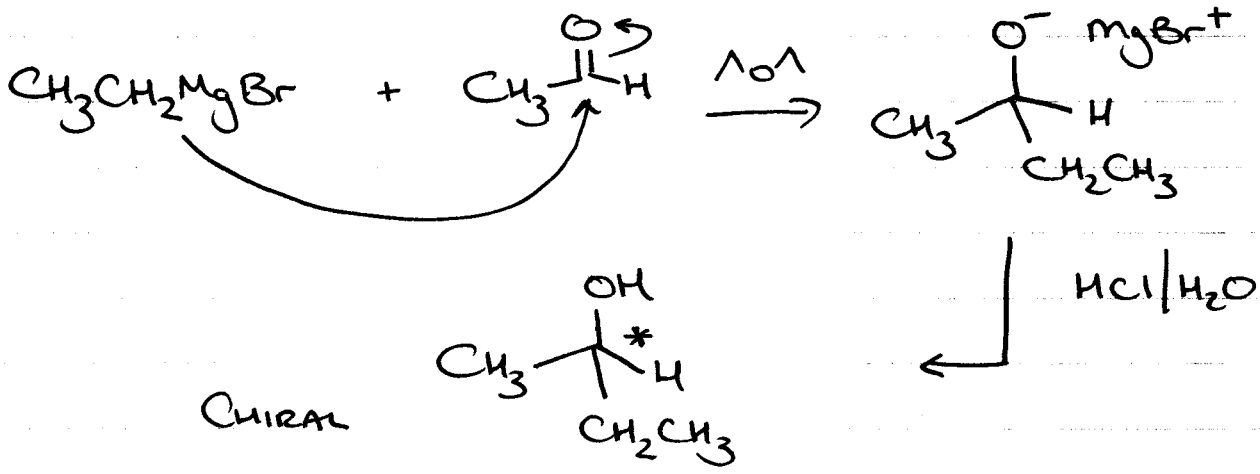
(i) FORMALDEHYDE 

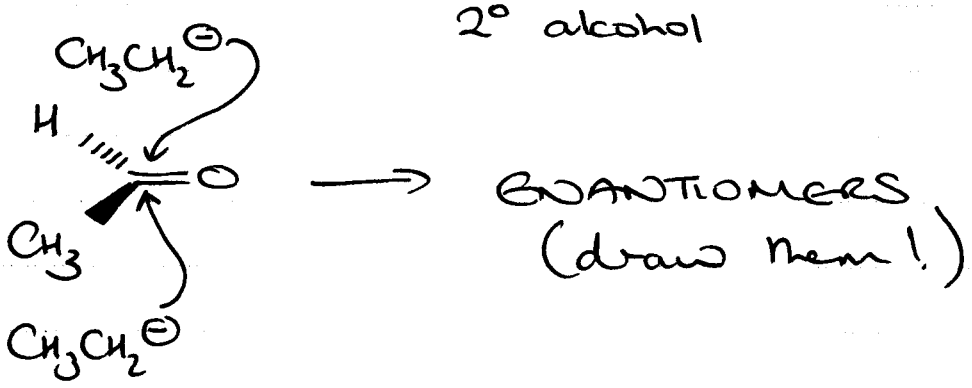



$CH_3CH_2OH$

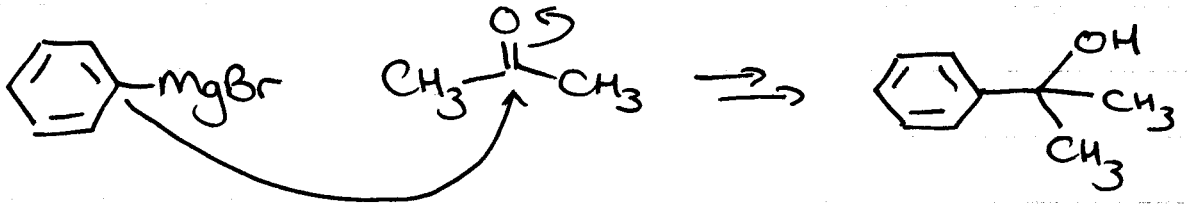
1° alcohol

(ii) ALDEHYDE (not $H_2C{=}O$)



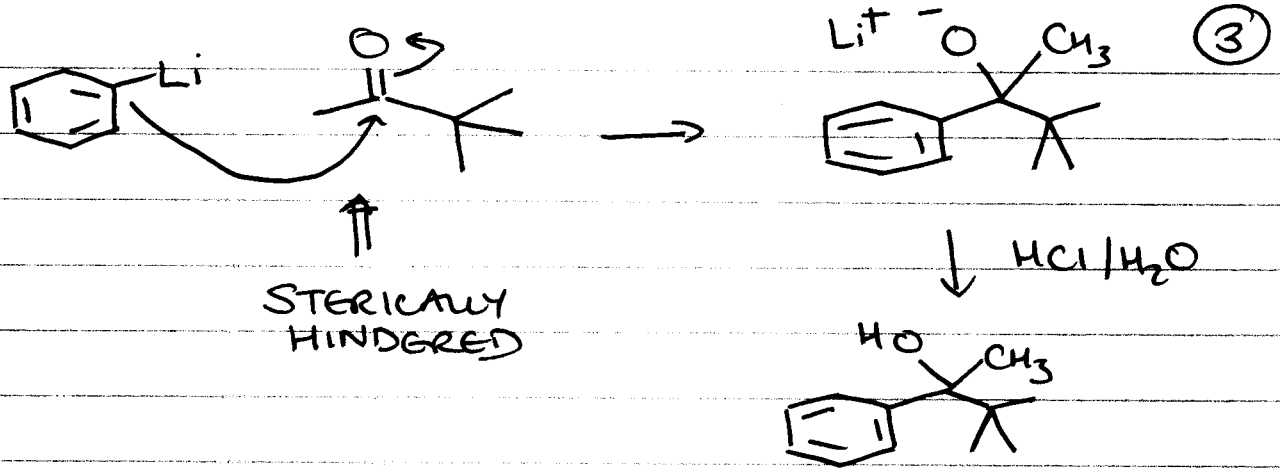




(iii) KETONES

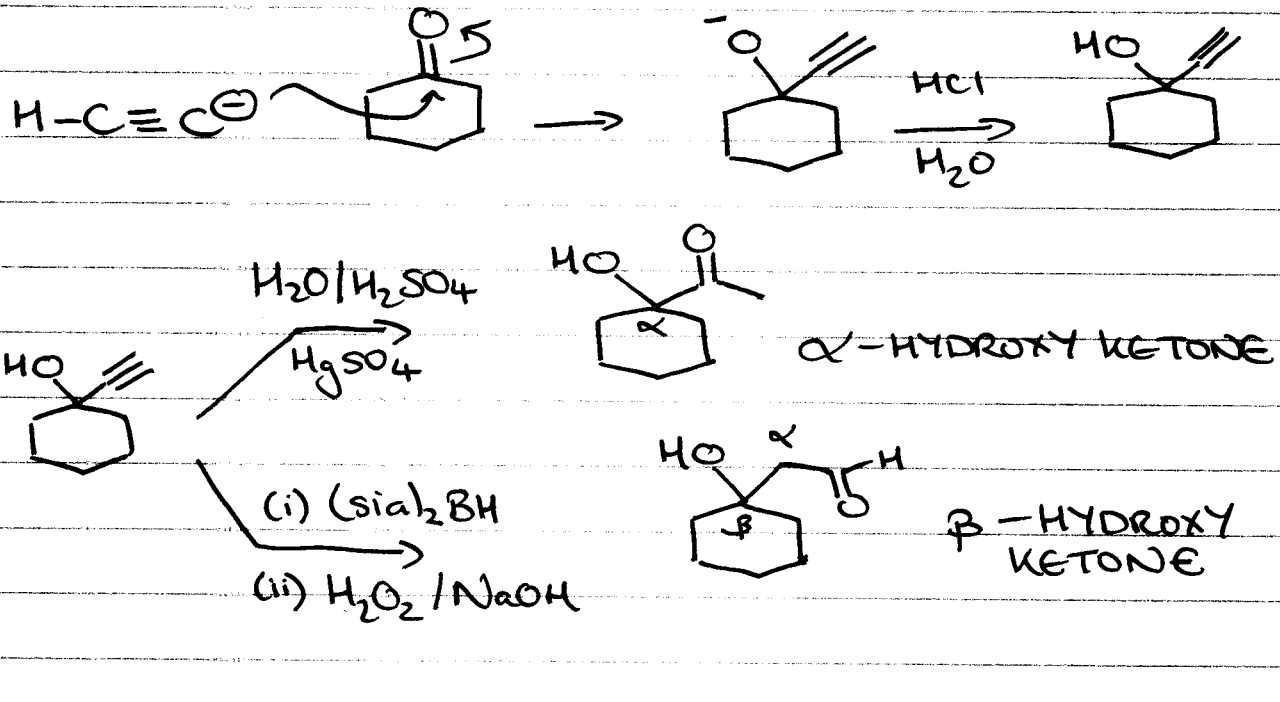



3° alcohol
(can also be chiral)

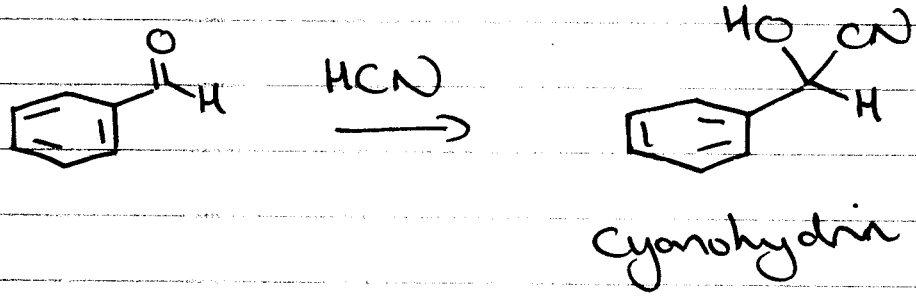
(B) ORGANOLITHIUMS
(more reactive than Grignards)
↳ use in an inert atmosphere



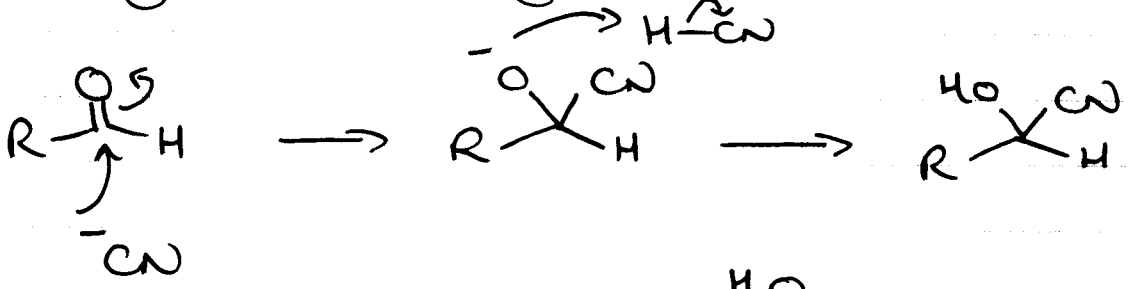

## ⑥ ALKYNYL ANIONS $R-C\equiv C^{\ominus}$




## ⑦ CYANIDE $CN^-$

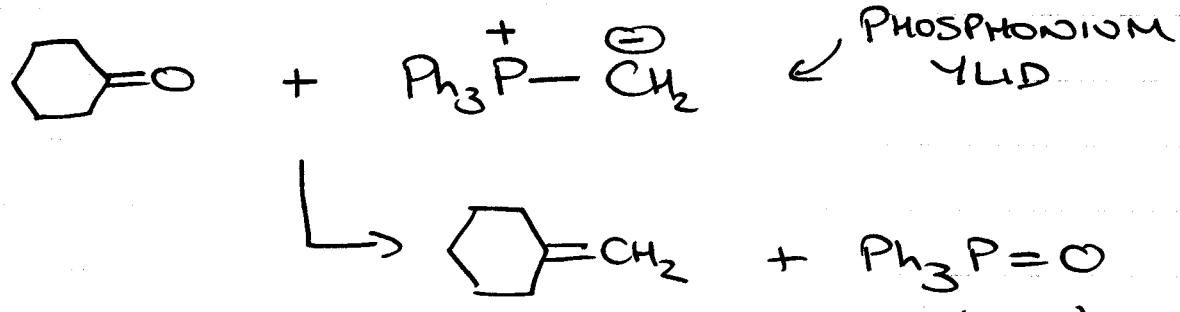


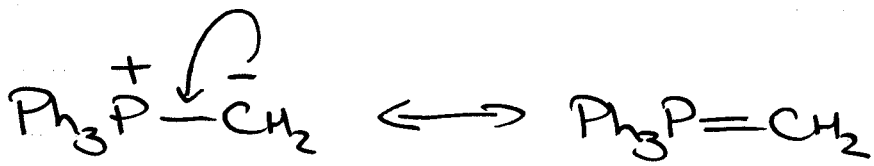
Usually base catalyzed (pH 10)



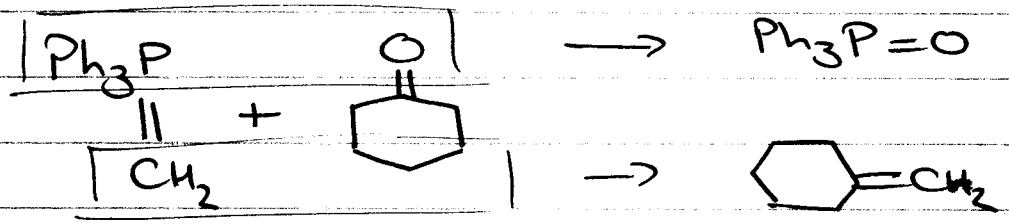

② WITTIG REACTION (1979 Nobel Prize w/ BROWN – $BH_3$)

$$C{=}O \longrightarrow C{=}C$$



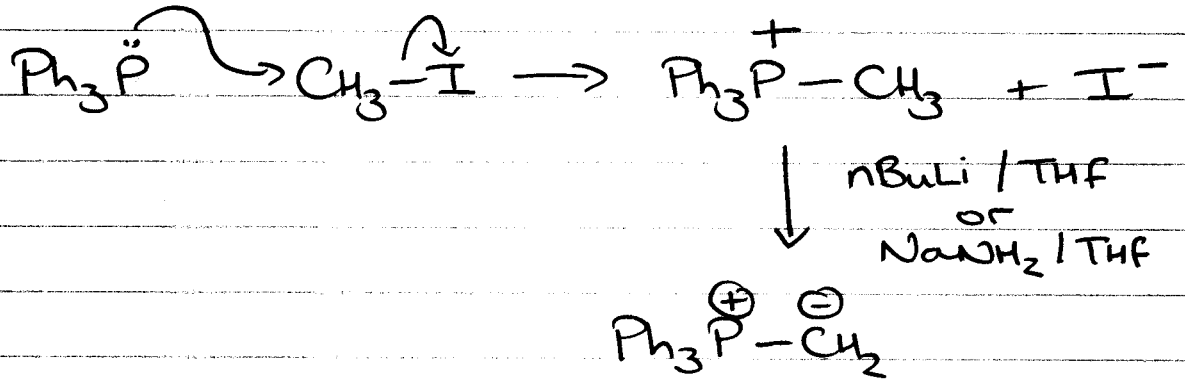



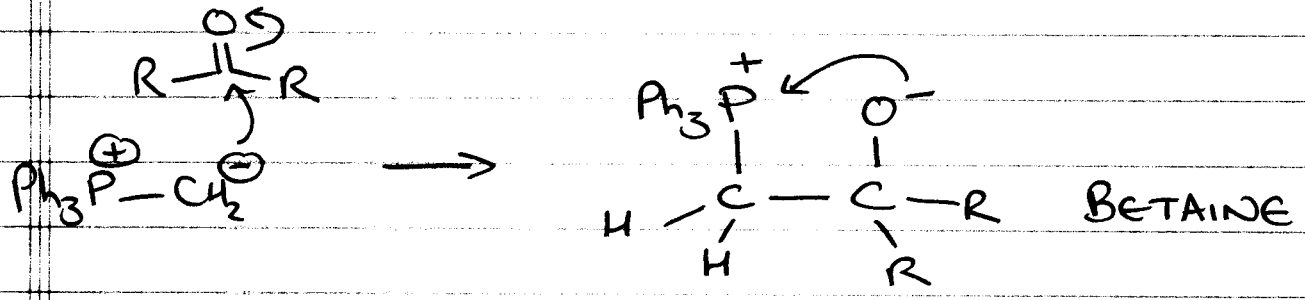
# A LITTLE LIKE METATHESIS

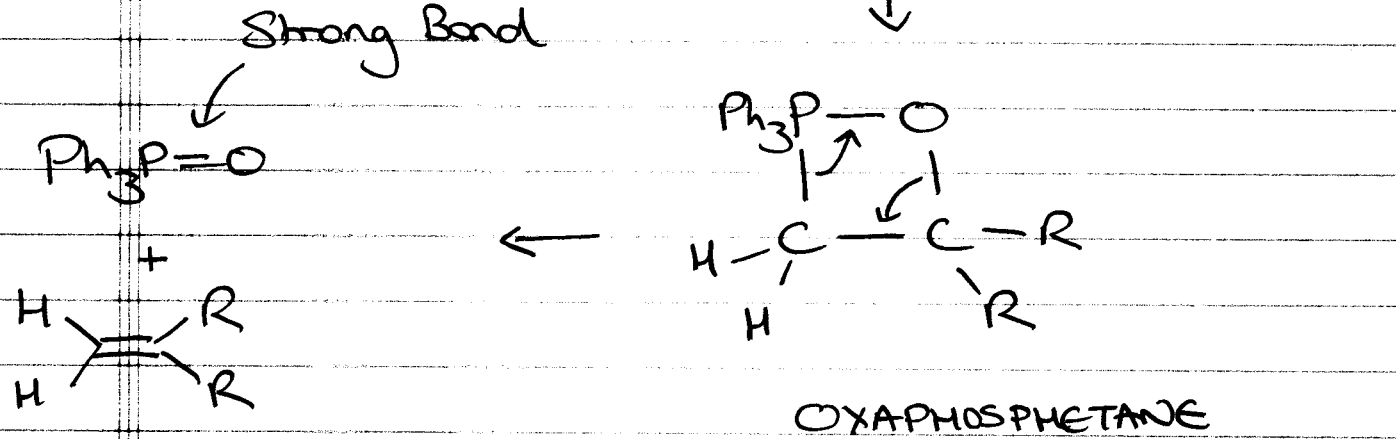


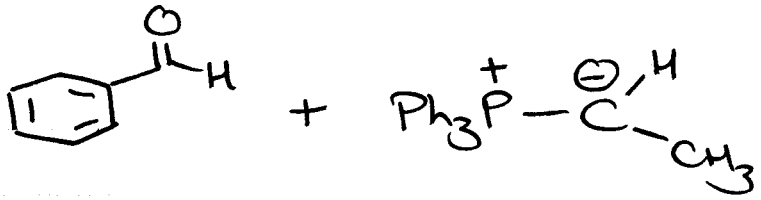

Switch ends of double bonds

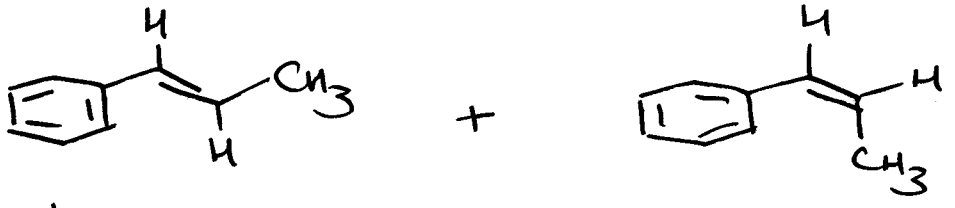
## The YLID



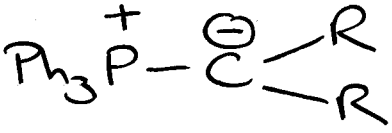




trans  cis

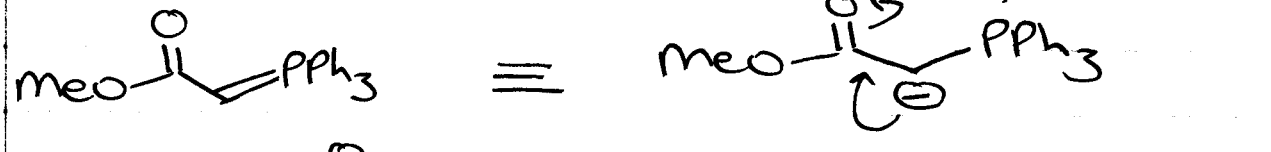
MIXTURE

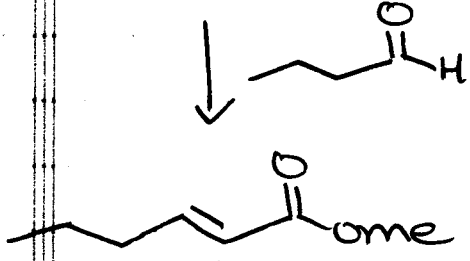
DRAW MECHANISM TO EXPLAIN THIS...



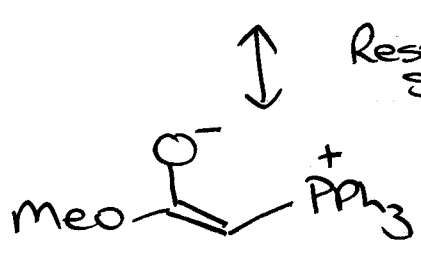
Unstabilized YLID

Stabilized YLID



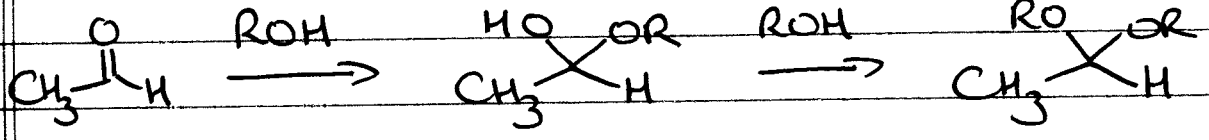


E ONLY (SELECTIVE)

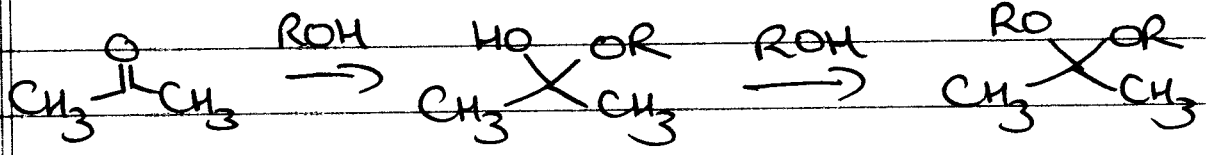


Resonance Stabilized

# OXYGEN NUCLEOPHILES



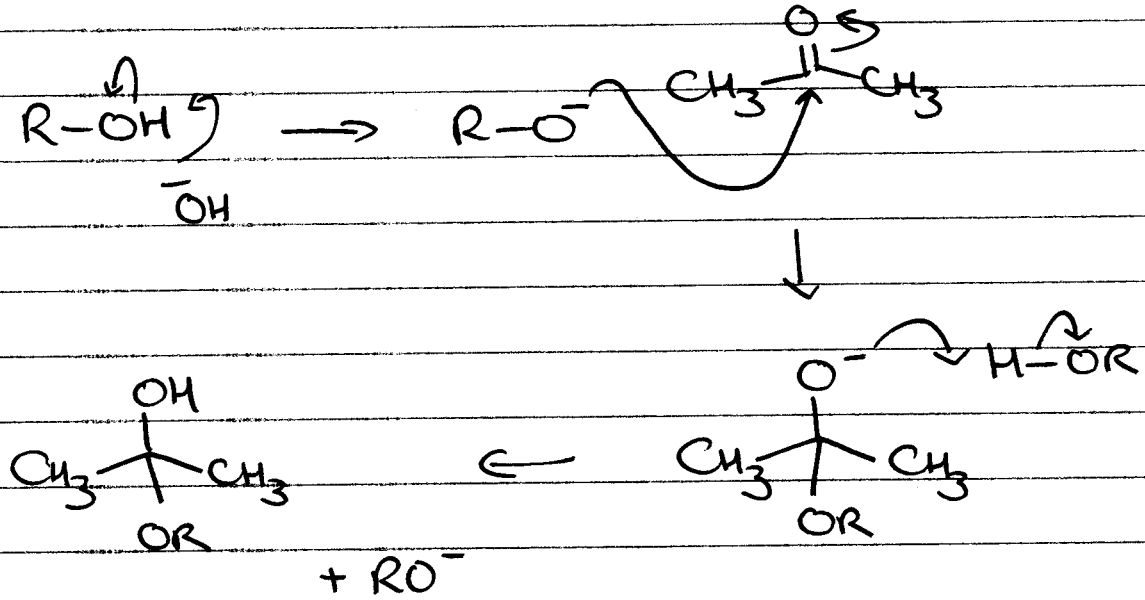

aldehyde hemiacetal acetal



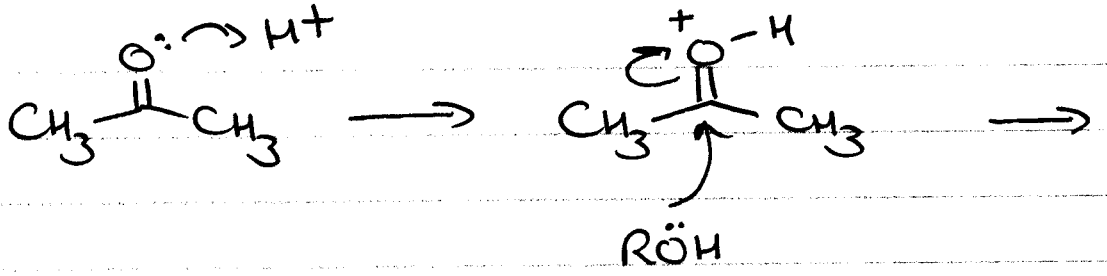

ketone hemiketal ketal

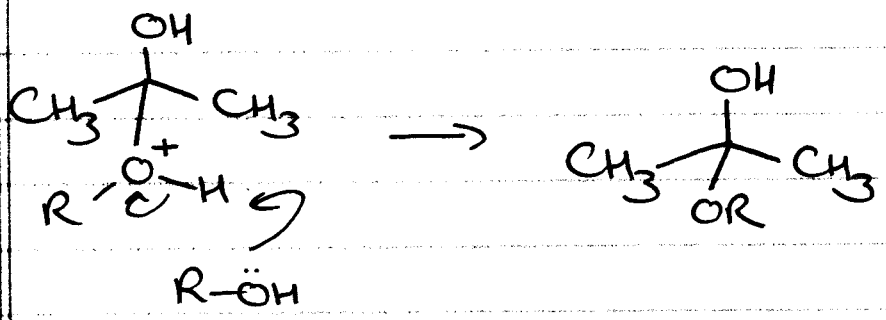
## — HEMIACETALS | HEMIKETALS

### (i) BASE CATALYZED



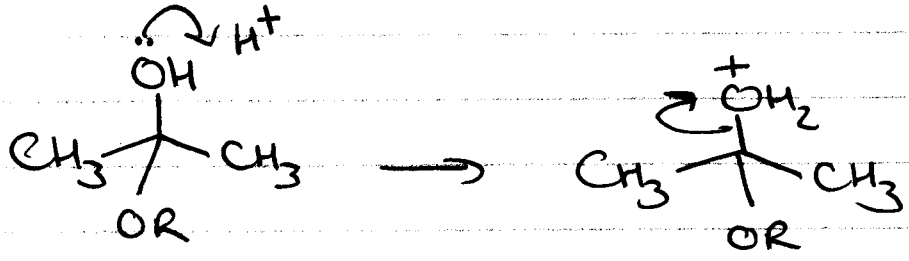

### (ii) ACID CATALYZED

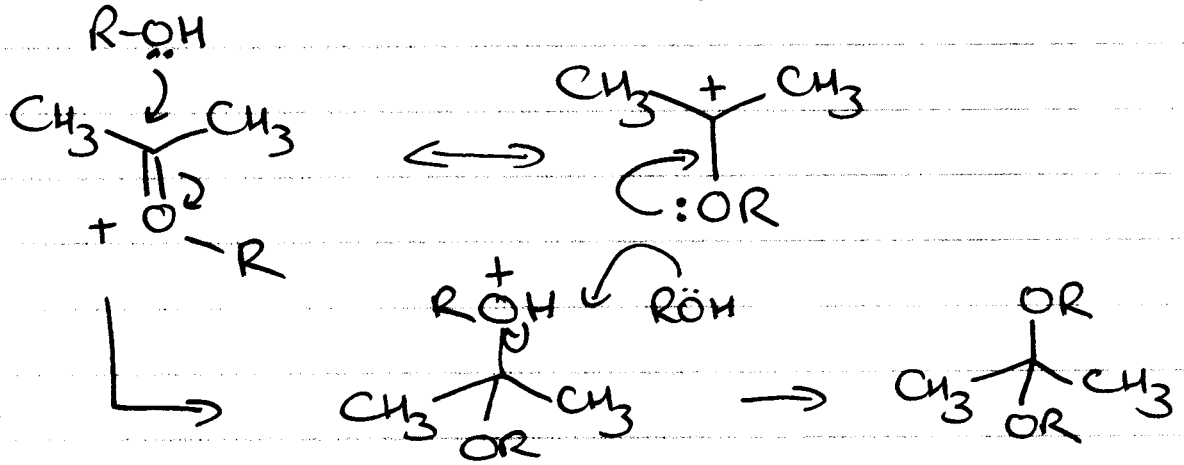


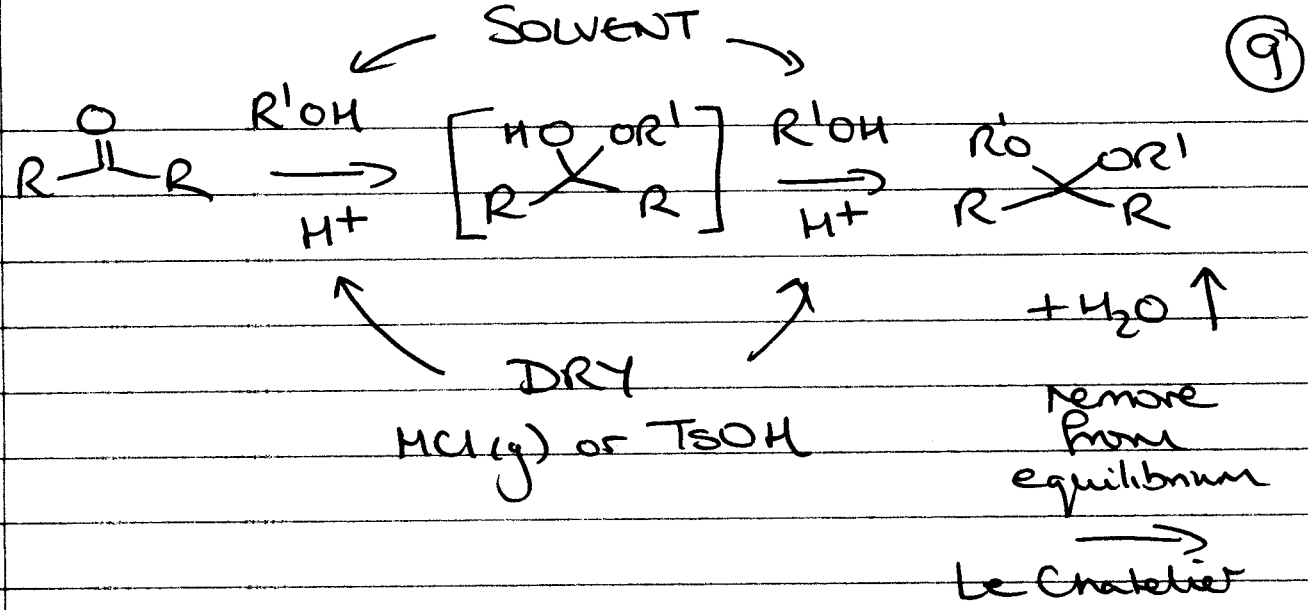




HEMIACETAL ⇒ ACETAL
HEMIKETAL ⇒ KETAL
} ONLY $H^+$ catalyzed (not base)

OH group not displaced by $Nuc^-$

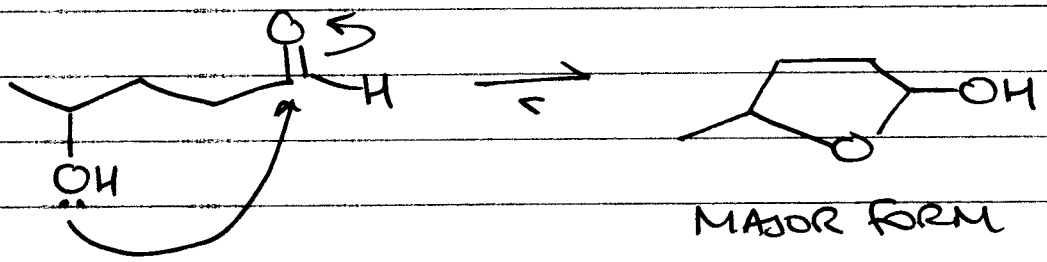


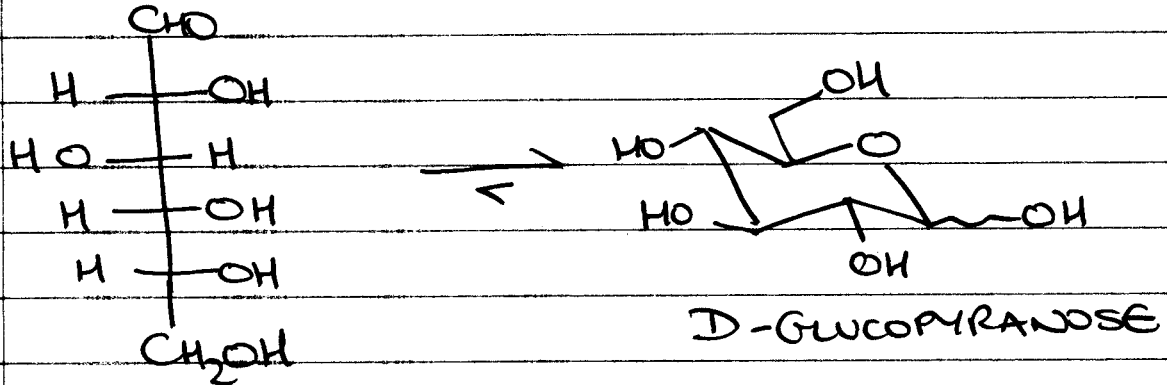



HEMIACETALS / HEMIKETALS
⇒ generally unstable

xcept for cyclic ones

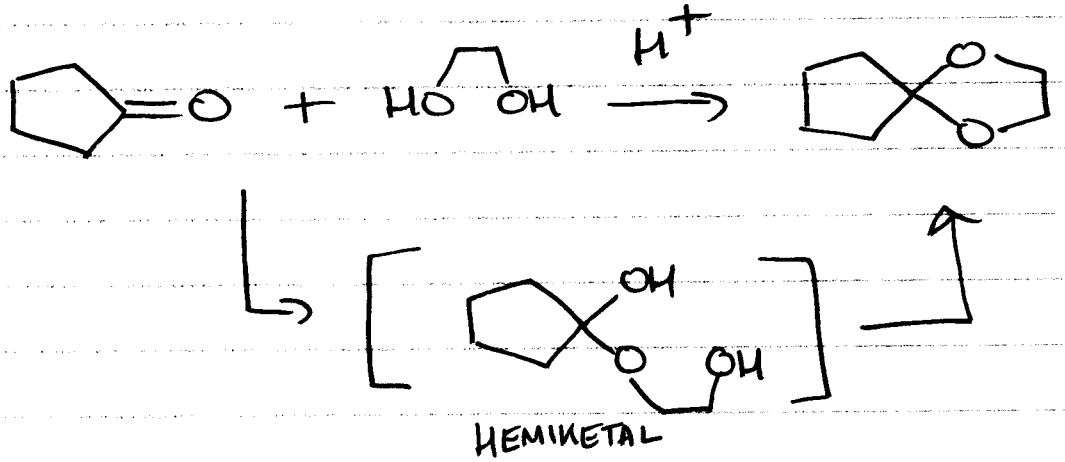



Important for 5/6 membered rings




D-Glucose (Straight Chain Fischer)

## Diols

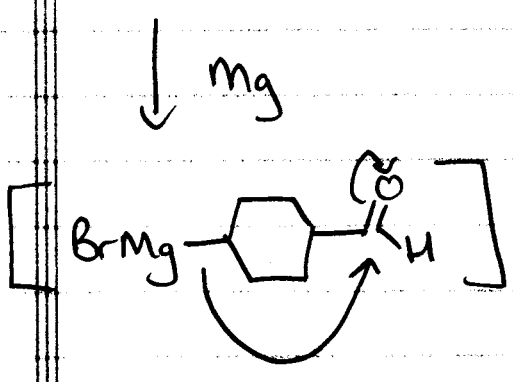



Like ethers, acetals/ketals stable to:

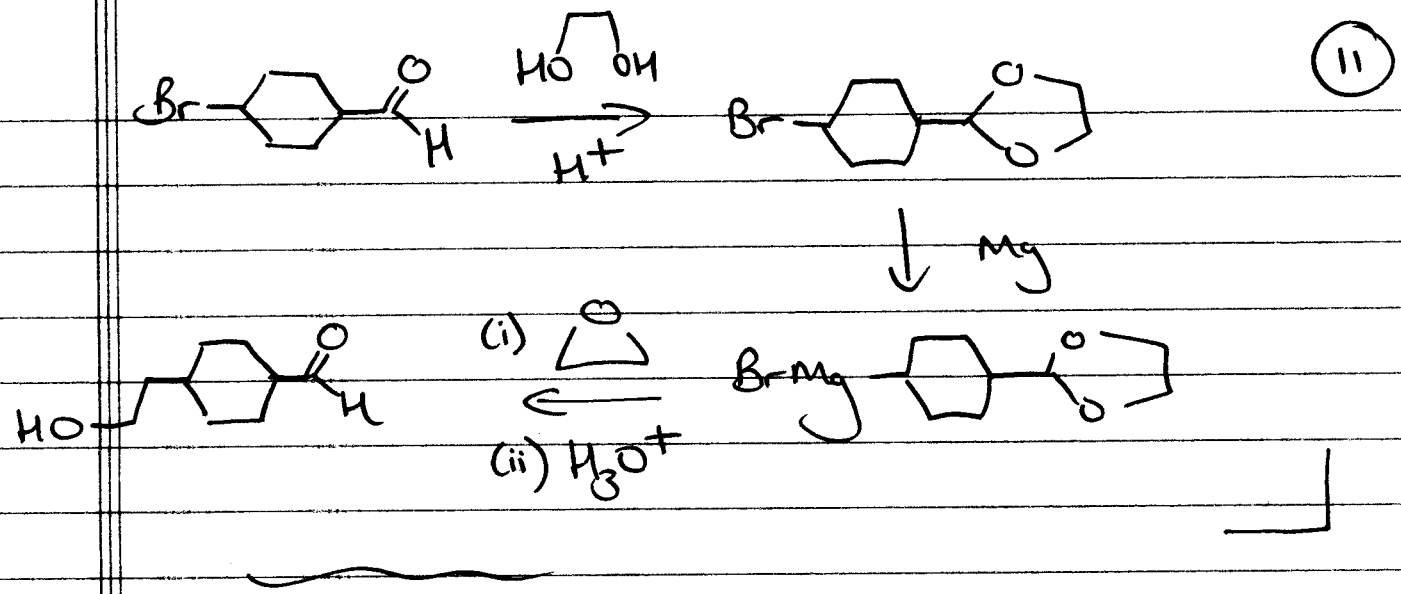
- bases
- organometallics (Grignard etc)
- non-acidic oxidants
- reduction

Cleaved w/ aqueous acid.

USED as protecting groups

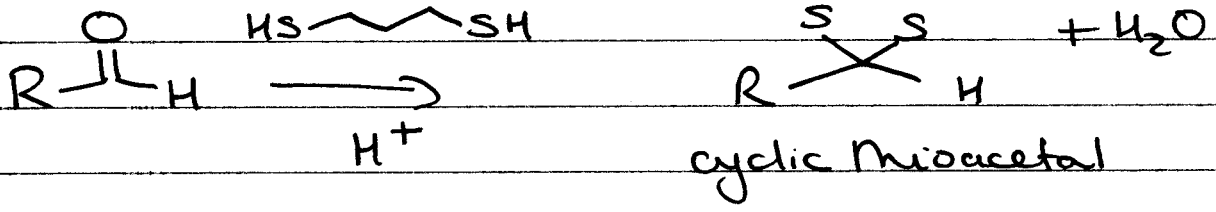

⟹ Self destructs



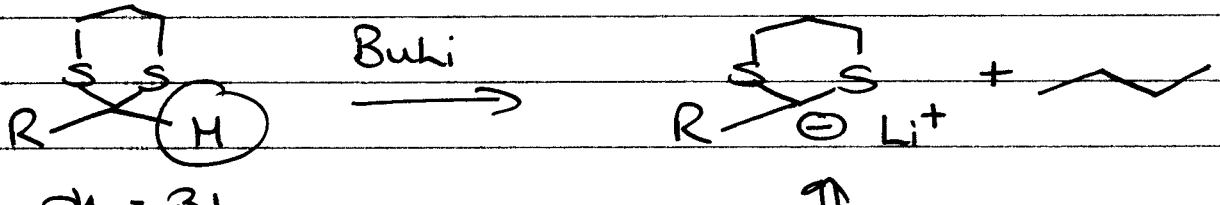

NEXT: SULFUR NUCLEOPHILES.

## ② SULFUR

1,3 dithiane



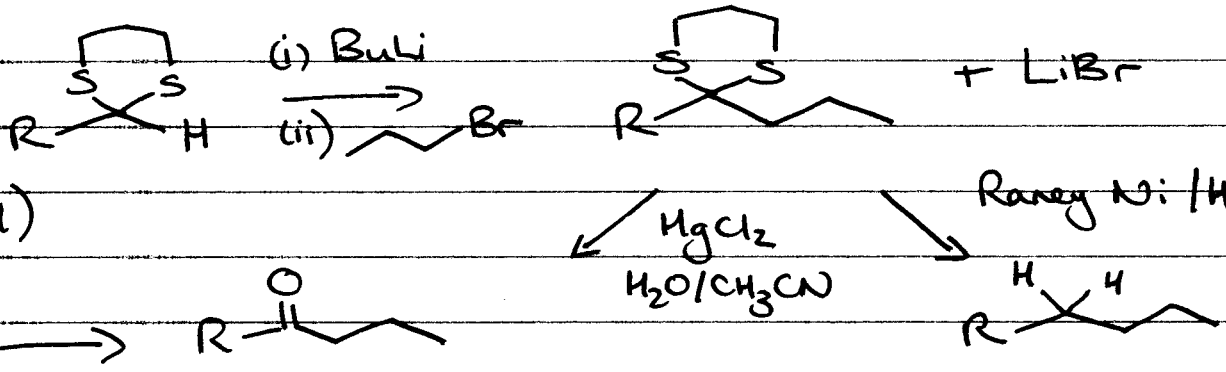

cyclic thioacetal



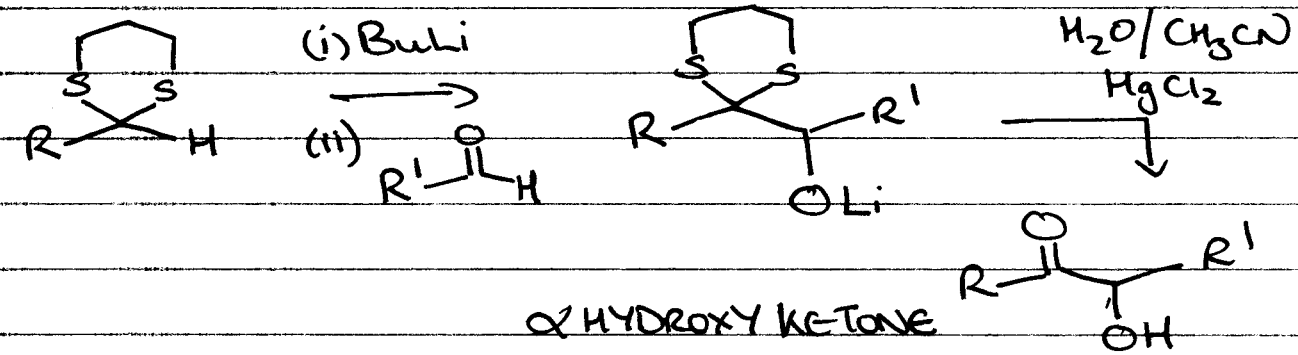

pKa = 31

nucleophilic

(i) $RCH_2Br$,  $S_N2$

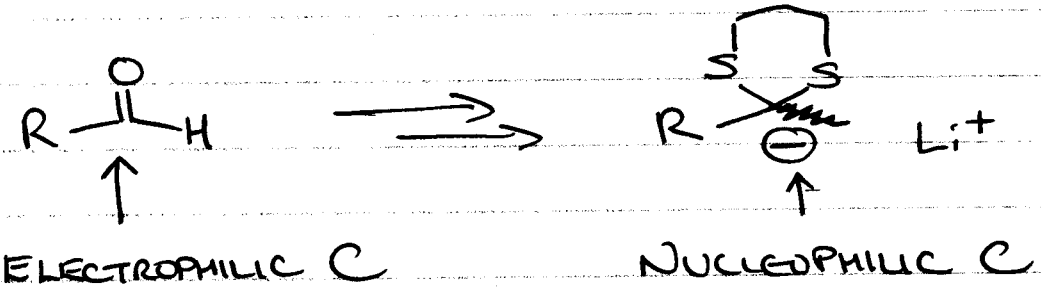



### (ii) Carbonyls




α HYDROXY KETONE

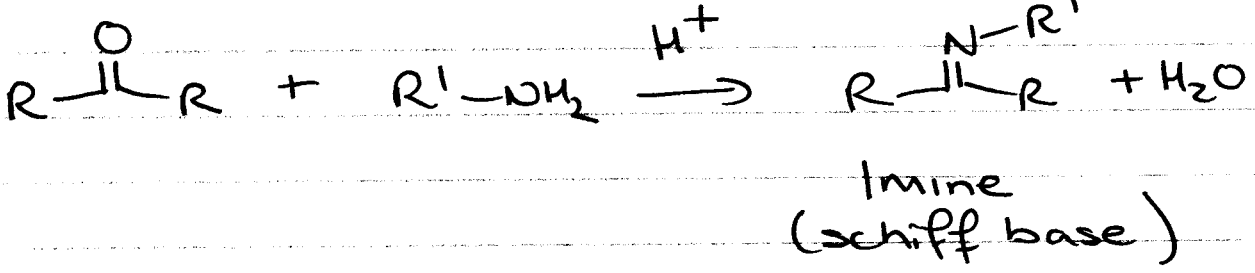
UMPOLUNG → POLE REVERSAL

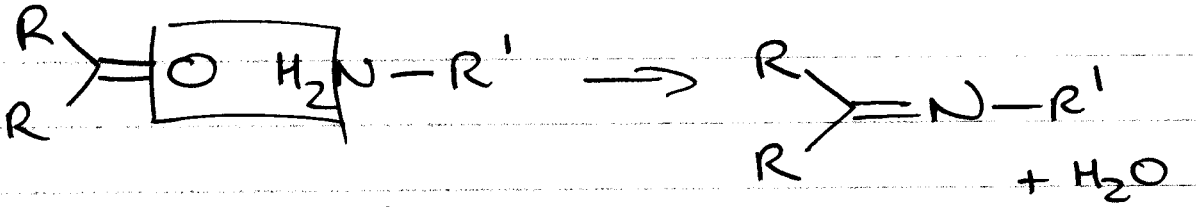


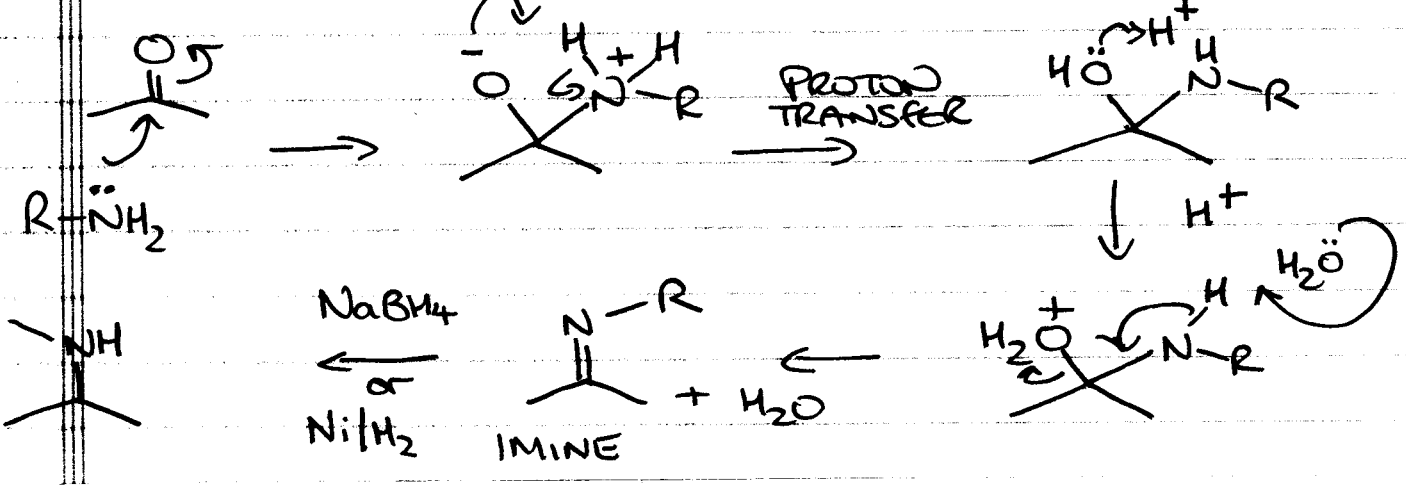

## (13) NITROGEN NUCLEOPHILES

1° AMINES ($NH_3$, $R-NH_2$ R = alkyl/aryl)

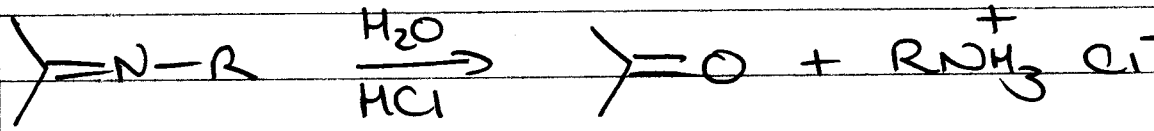
Reacts w/ aldehydes & ketones



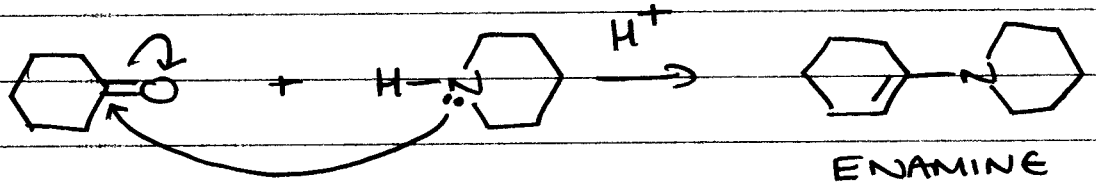


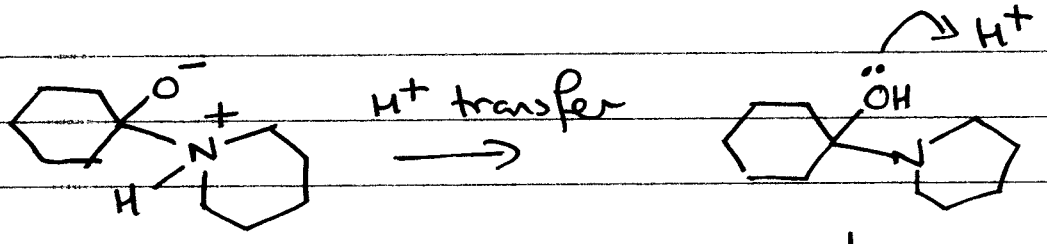
## ACID CATALYZED HYDROLYSIS

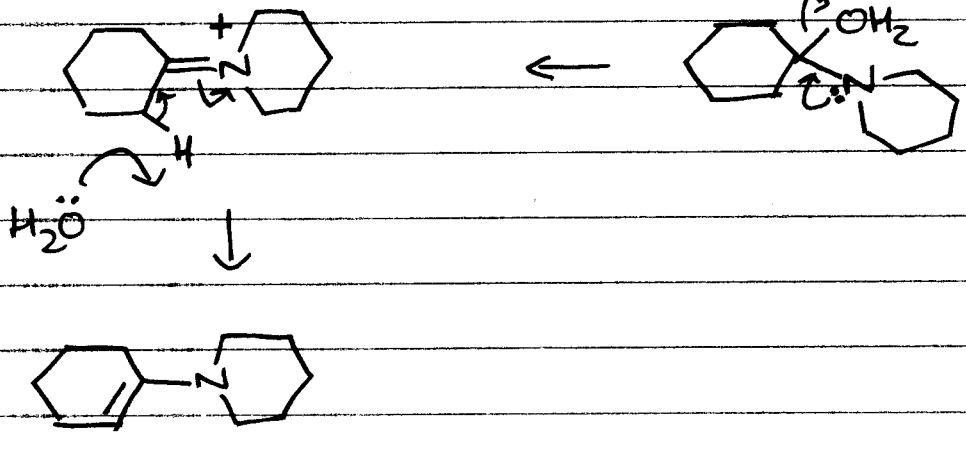



Work out mechanism

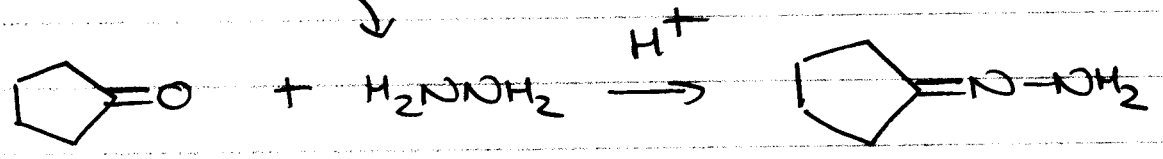
## SECONDARY AMINES



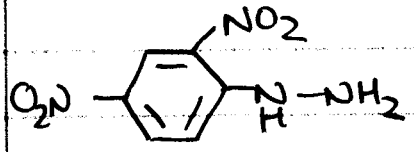



HYDRAZINE



HYDRAZONE



2,4 DINITROPHENYLHYDRAZINE

makes crystalline derivs of liquid aldehydes/ketones ⇒ mp

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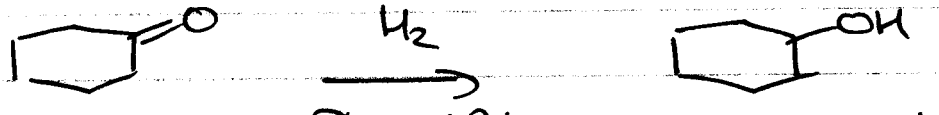
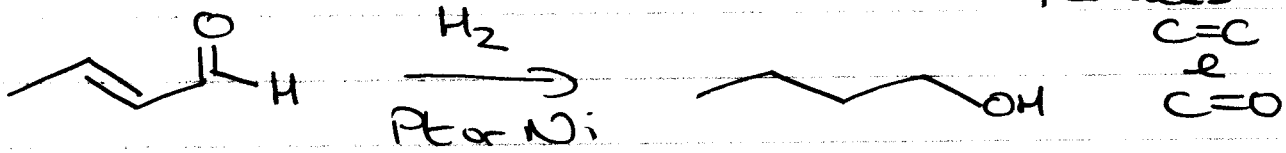
NEXT UP : OXIDATION/REDUCTION

REDUCTION

(i) CATALYTIC HYDROGENATION

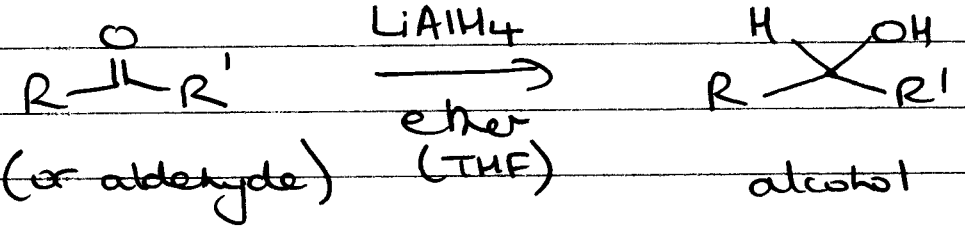


Ketone (or aldehyde)



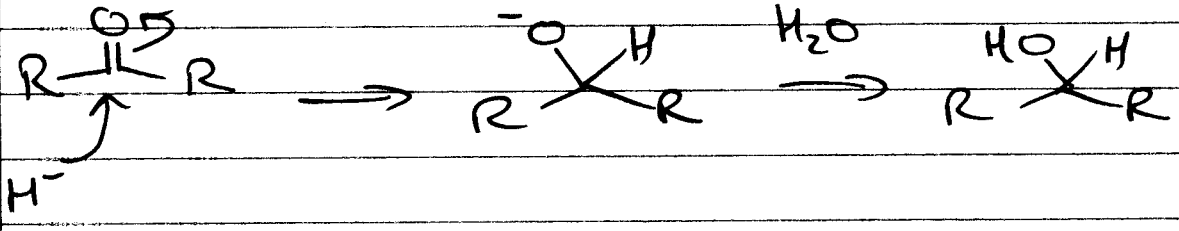
reduces C=C & C=O

(iii) METAL HYDRIDE

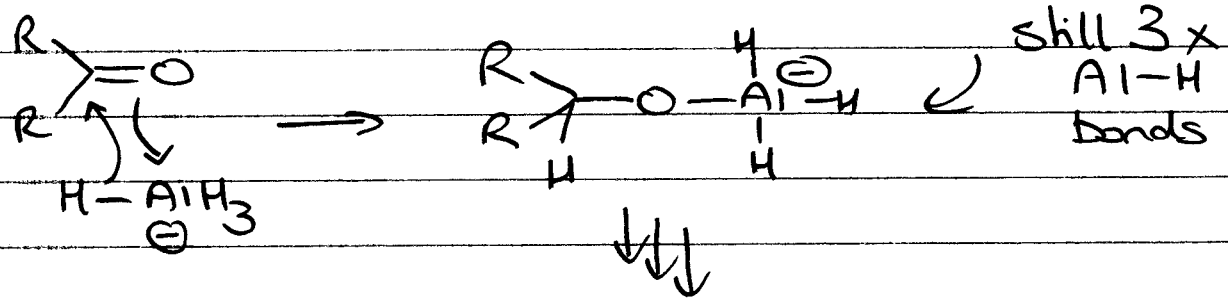



if $R \neq R'$, product is a racemic mixture

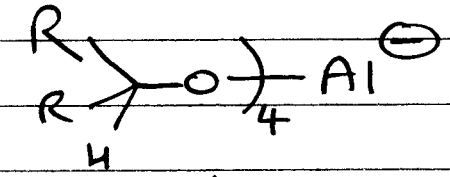
$LiAlH_4$ = "$H^-$"

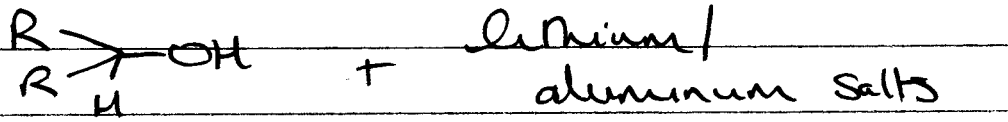


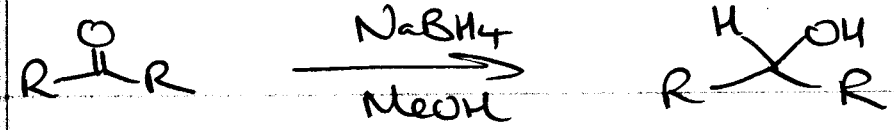

not actually $H^-$, e.g. NaH is not REDUCING




TETRAALKYL ALUMINATE

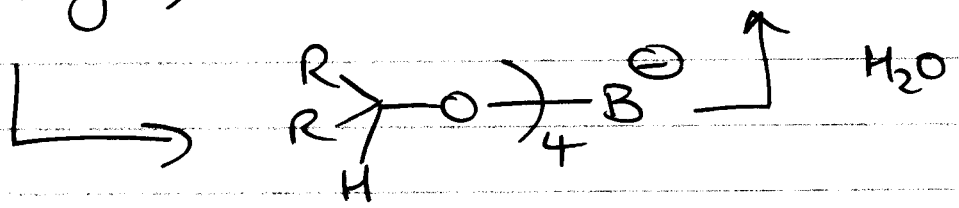




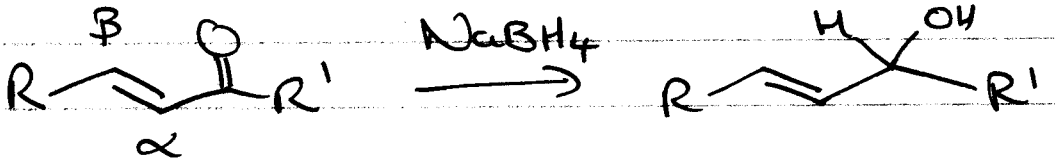



alcohol

(or aldehyde)

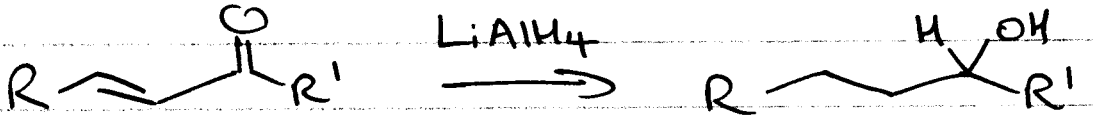



TETRAALKYLBORATE



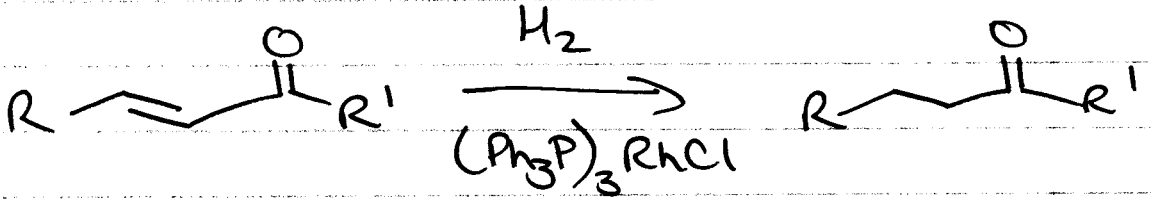

α-β unsaturated

reduces C=O selectively




reduces C=C and C=O

NOTE:




reduces C=C selectively

# Lec 21

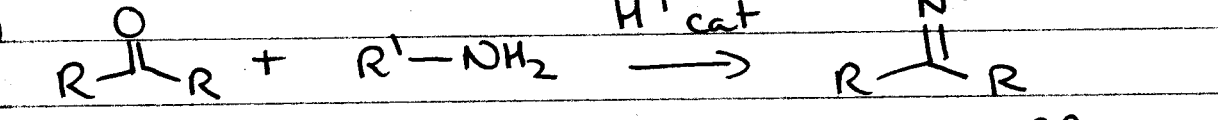
MIDTERM ② LOW 6 HIGH 83 AV 38

HMK → HANDOUTS & MIDTERM 2

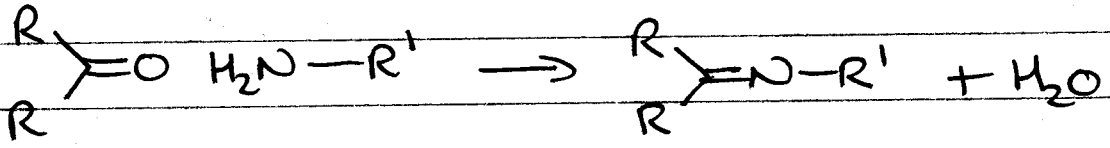
① AMINES rxt w/ C=O

② REDUCTION

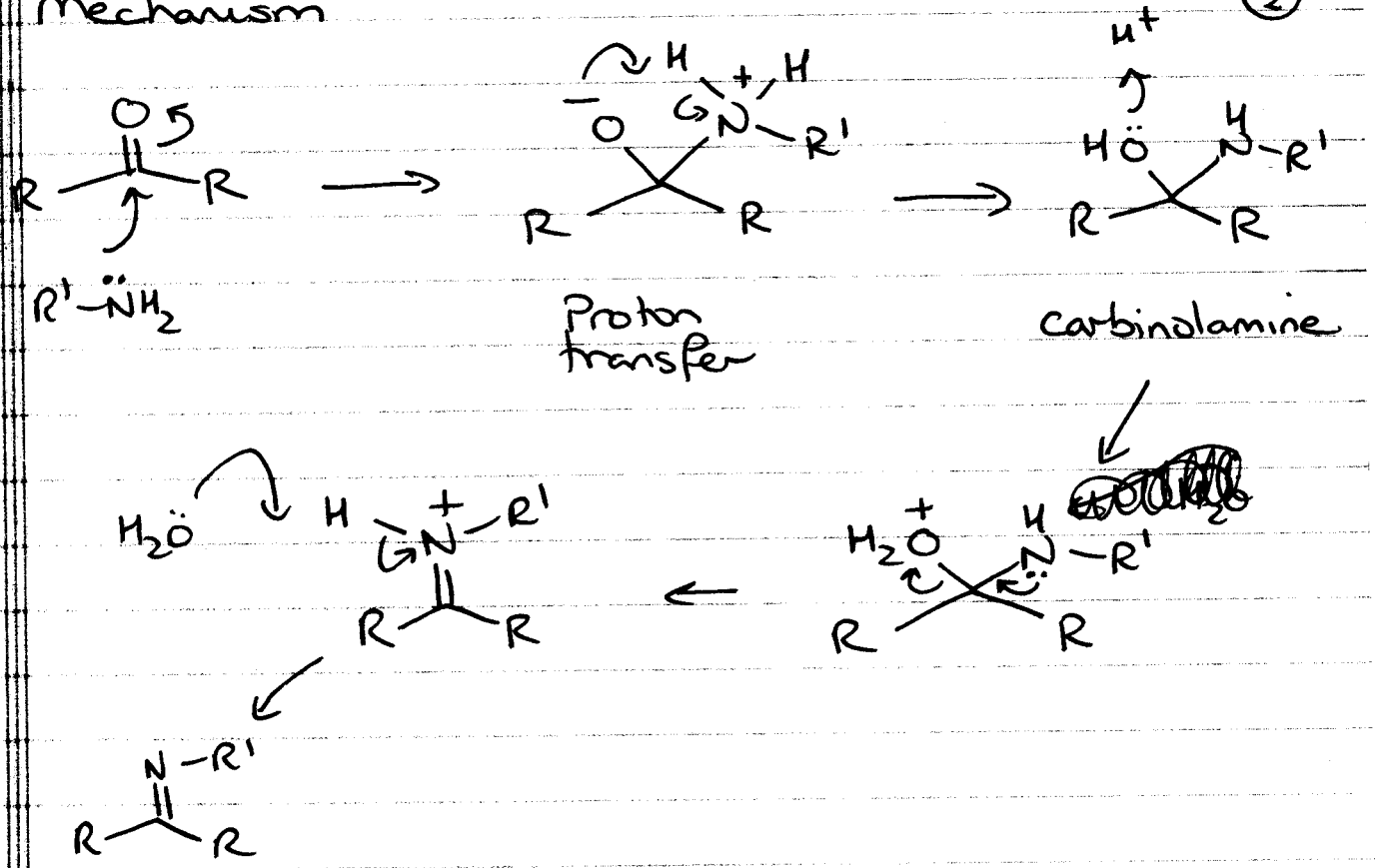
③ OXIDATION

① 

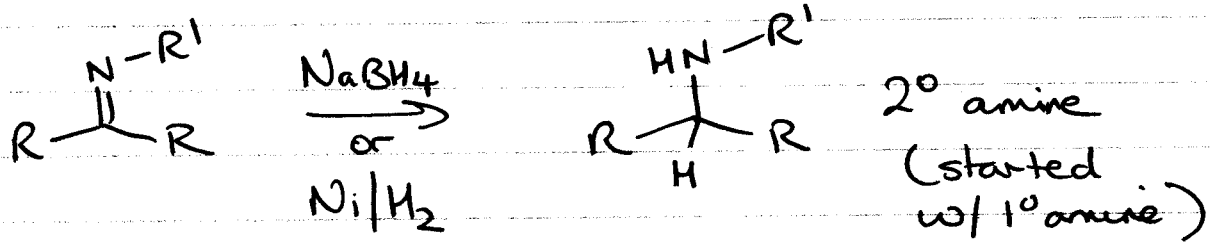

Imine / Schiff base



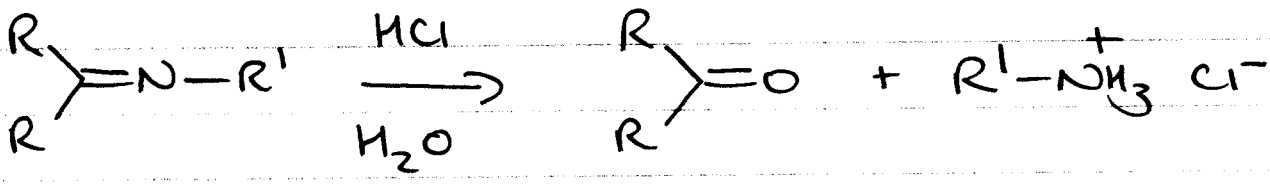
## Mechanism



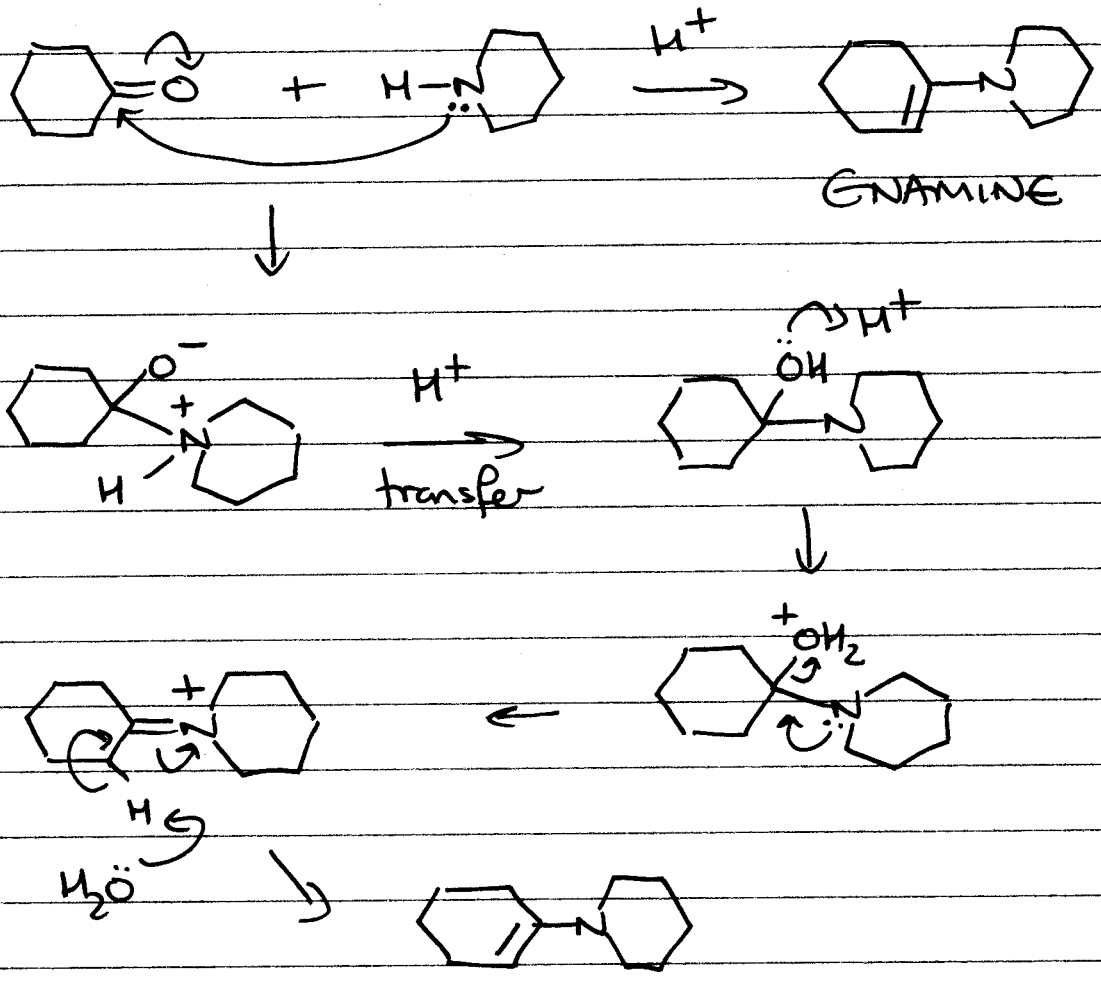

## REDUCTION of IMINES



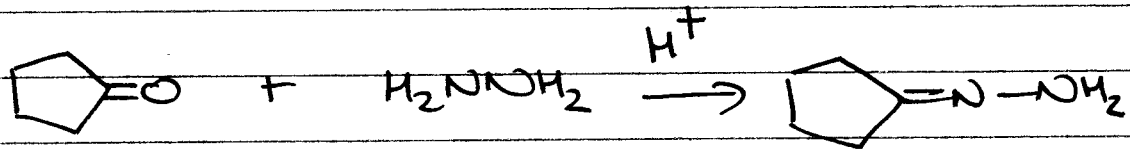

## ACID cat HYDROLYSIS

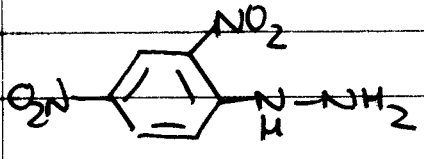


## SECONDARY AMINES




## HYDRAZINE



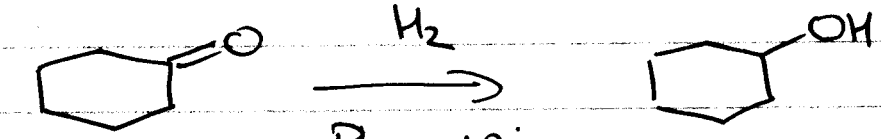




2,4-DINITROPHENYLHYDRAZINE

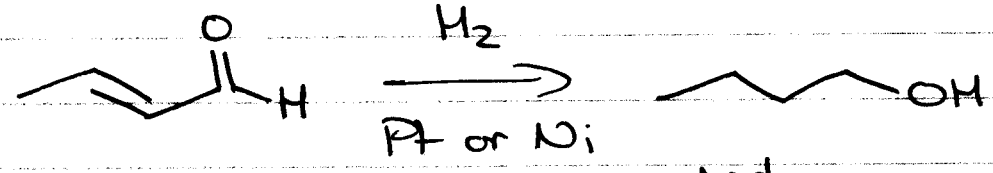
makes crystalline derivatives of liquid aldehydes and ketones ⟹ mp

## (2) REDUCTION

### (i) CATALYTIC HYDROGENATION

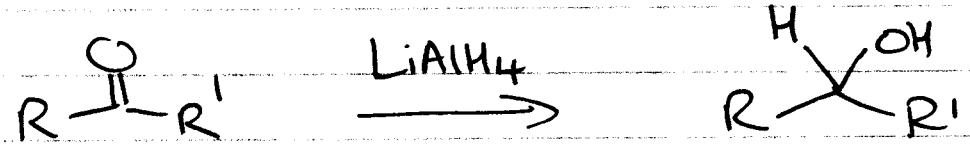



ketone (or aldehyde) → alcohol




reduces C=C & C=O

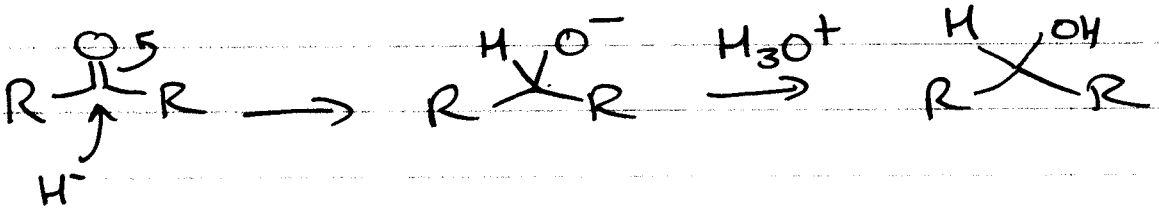
### (ii) METAL HYDRIDE




(or aldehyde) → alcohol

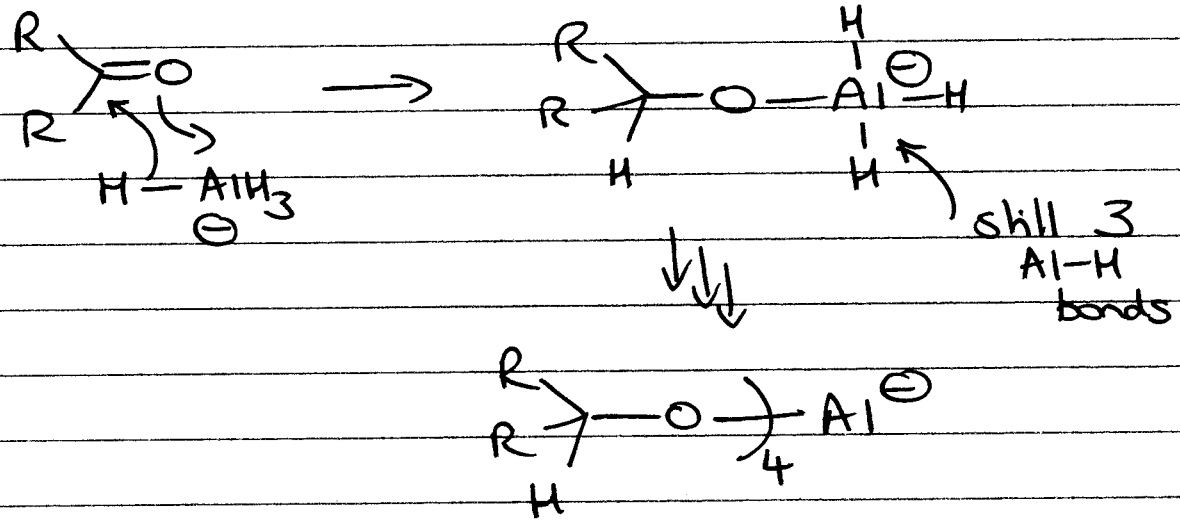
if $R \neq R'$, product is a racemic mixture

$LiAlH_4$ = "$H^-$"



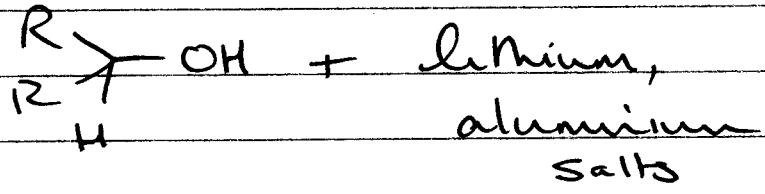

not actually $H^-$, eg. NaH is not REDUCING

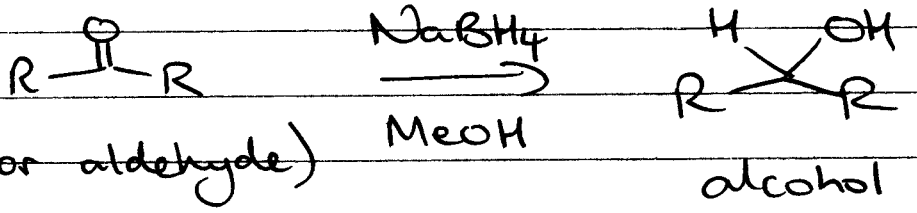
MECHANISM

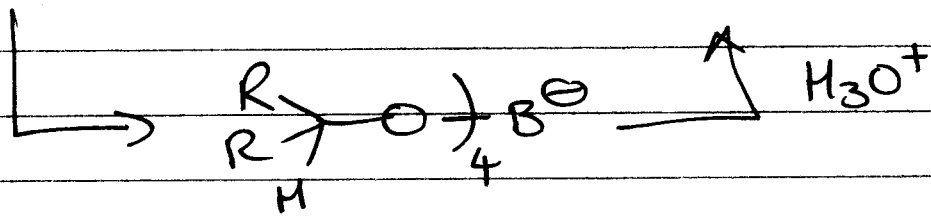



TETRAALKYLALUMINATE

$\downarrow H_3O^+$

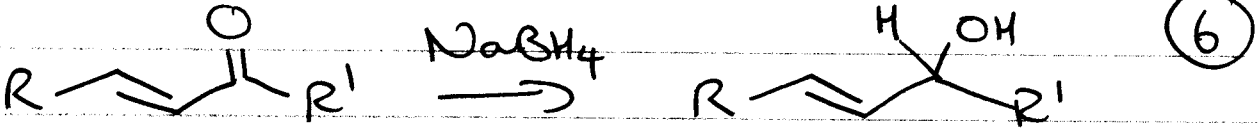


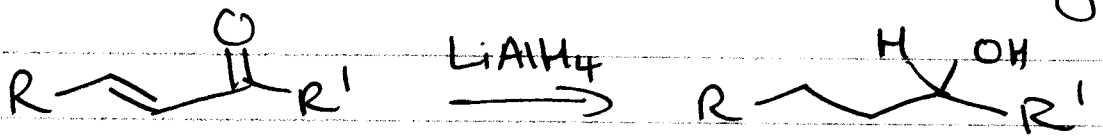

TETRAALKYL BORATE

(work out mechanism for homework)



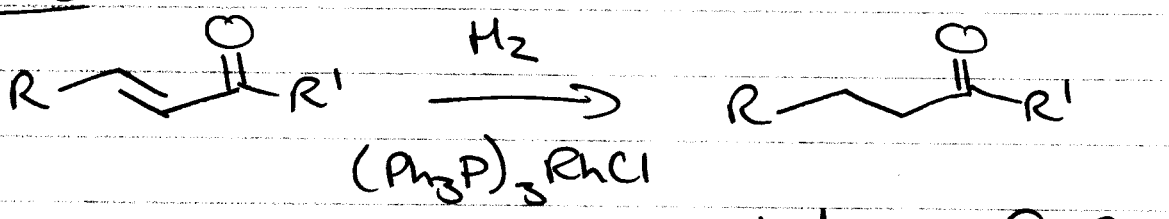

α-β unsaturated

Reduces C=O selectively

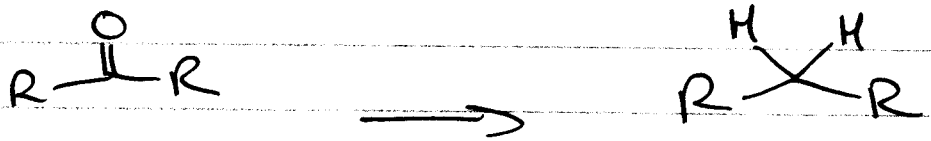



Reduces C=C and C=O

NOTE:

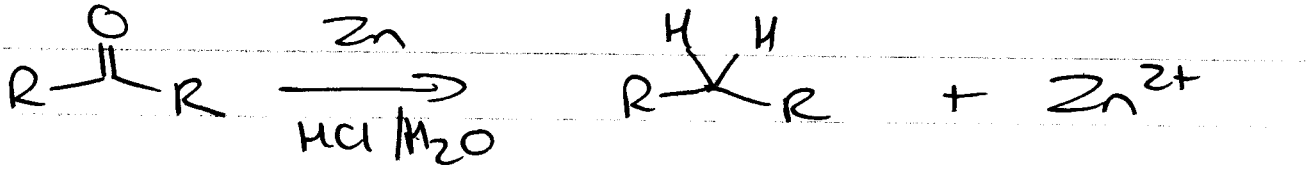



Reduces C=C selectively



or aldehyde

CLEMMENSEN (acidic conditions)



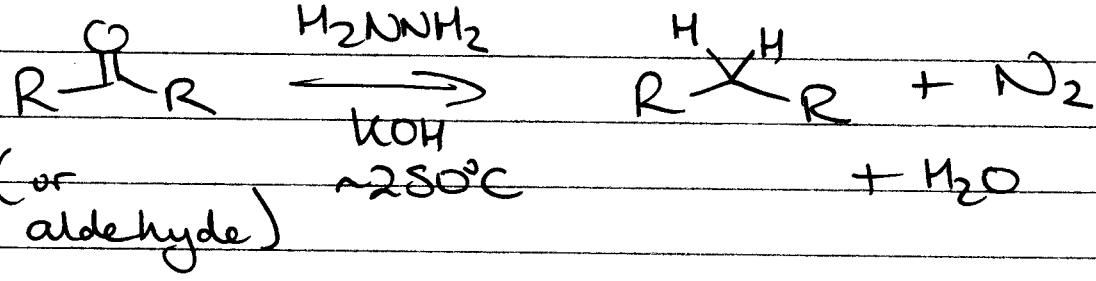

C=O reduced

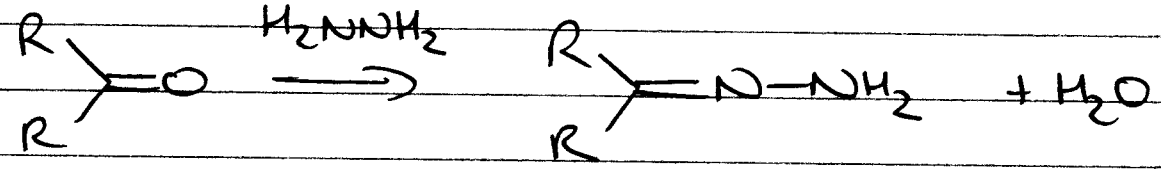
Zn is oxidized

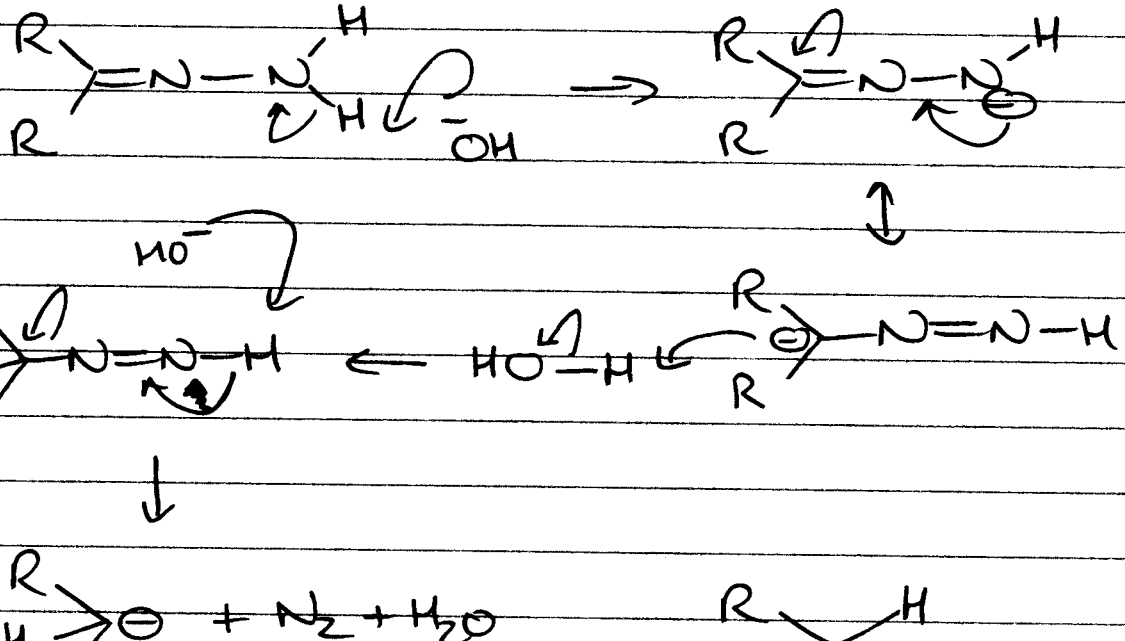
Heterogeneous rxn → do not worry about the mechanism

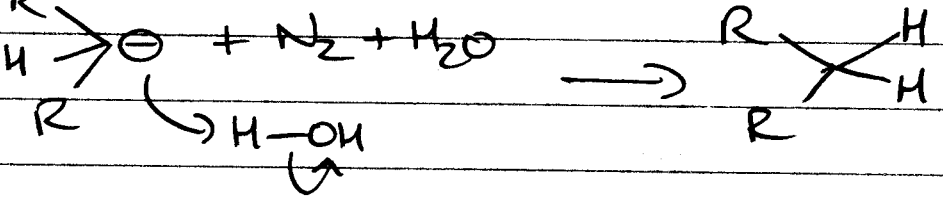
Cannot be used for acid sensitive cmpds

WOLFF-KISHNER (Basic conditions)



milder conditions

DMSO (solvent) / $NH_2NH_2$ / $^tBuO^- K^+$ (base)

(3) OXIDATION

$RCH_2OH \xrightarrow{ox} RCHO \xrightarrow{ox} RCO_2H$

$R-CHO \xrightarrow{H_2CrO_4} RCO_2H$

$R-CHO \xrightarrow[\text{or } H_2O_2]{O_2} RCO_2H$

$R-CHO \xrightarrow{Ag(1)} RCO_2H + Ag$ (METAL)

EXPENSIVE

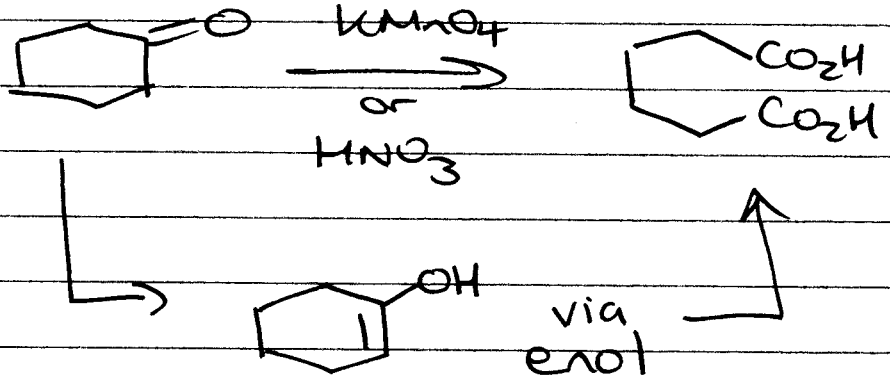
$Ag_2O$ or $Ag(NH_3)_2^+ NO_3^-$

TOLLENS REAGENT

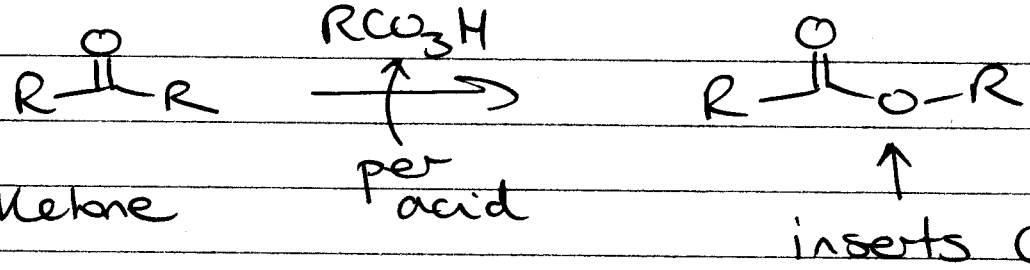
Often done for Ag as PRODUCT

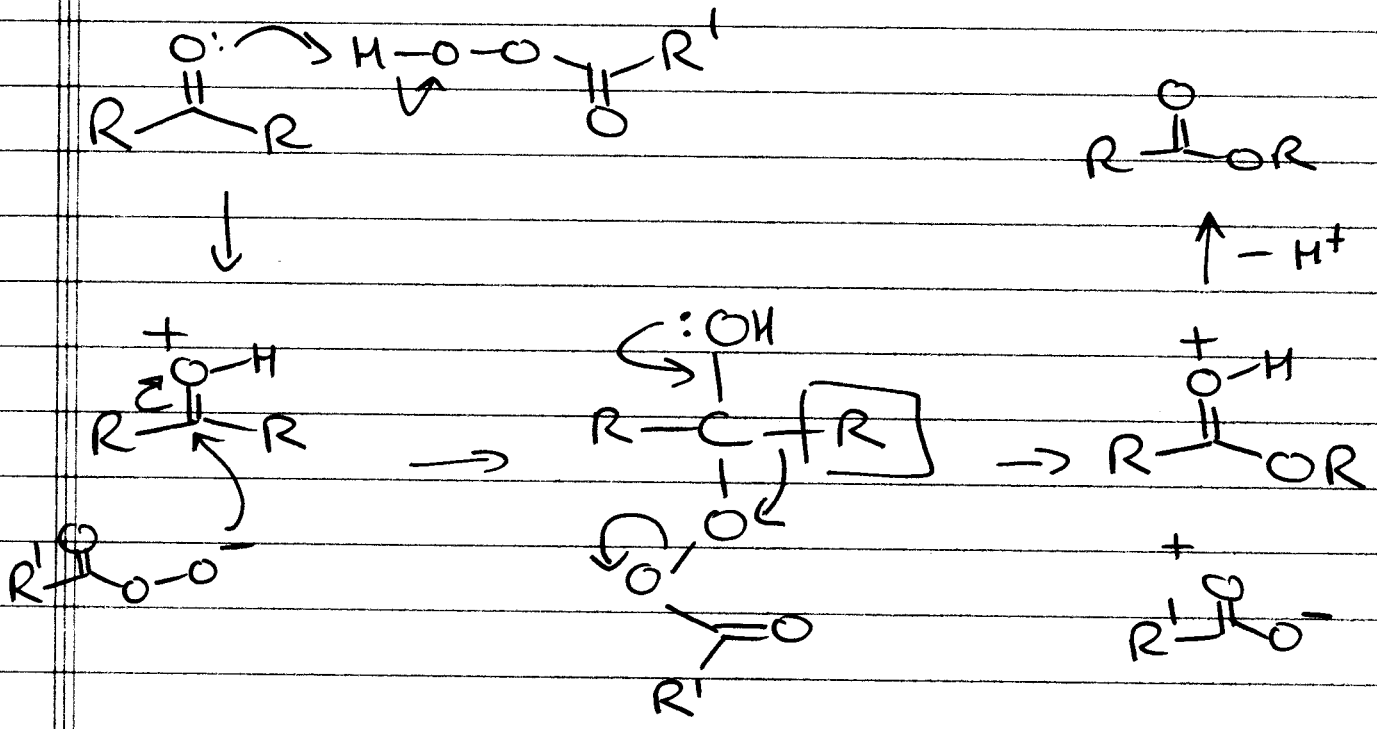
$\Rightarrow$ SILVERING GLASSWARE (MIRRORS)

## KETONES (harsh conditions)



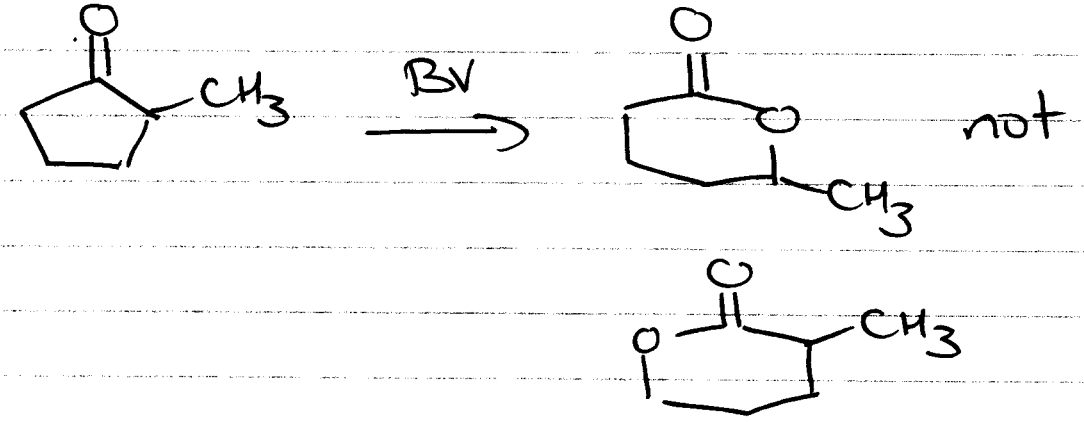

## BAEYER VILLIGER OXIDATION



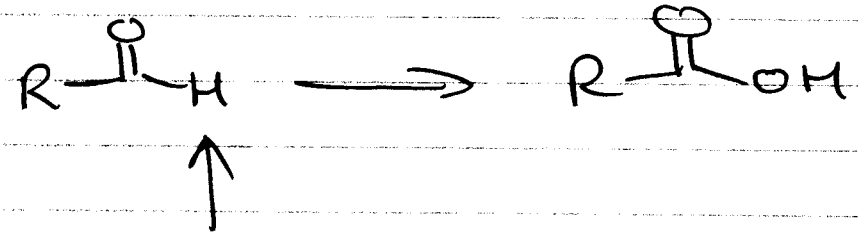
# MIGRATION RATES

$3^\circ > 2^\circ \sim Ar > 1^\circ > CH_3$




→ $C^+$ character in TS

<u>NOTE</u> for ALDEHYDES




H <u>MIGRATES</u>

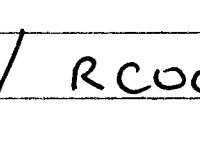
(1) HMK 16.54 – 16.68
+ any other Ch16 questions (ignore sects 16.11/12 for now)
17.2, 3, 15, 16, 18-31
(2) ALL CNSI summaries due by last day of class
(3) FINAL DEAL

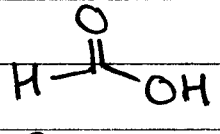
---

(1) C=O OXIDATION
(2) CARBOXYLIC ACIDS
- STRUCTURE
- PHYSICAL PROPERTIES
- PREPARATION
- REACTIONS

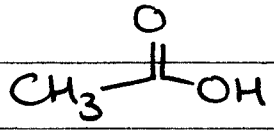
---

(2) STRUCTURE

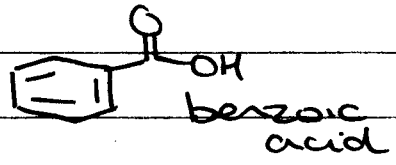
$R-CO_2H$ / RCOOH / 



formic acid



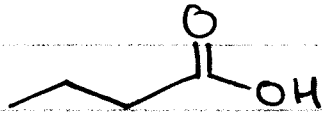
acetic acid (AcOH) →  acetyl group




benzoic acid

Ch 17 – 'COMEDY CHAPTER'

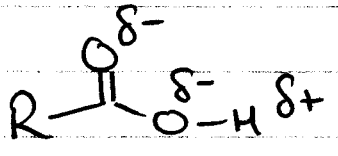
1670 – formic acid first obtained in 1670 from the "destructive distillation of ants"



BUTANOIC ACID ($C_4$)

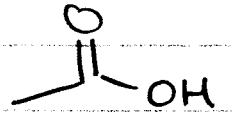
"Butanoic acid is found in stale perspiration and is a major component of 'locker room odor'. Pentanoic acid smells even worse, and goats, which secrete $C_6$, $C_8$, $C_{10}$ acids, are not famous for their pleasant odors."

Other physical properties:



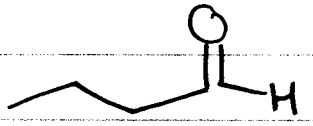
very polar

Boiling points



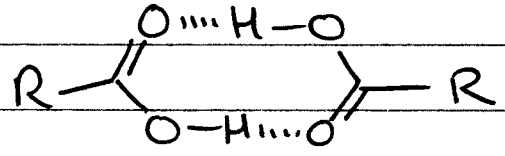
118°C

97°C

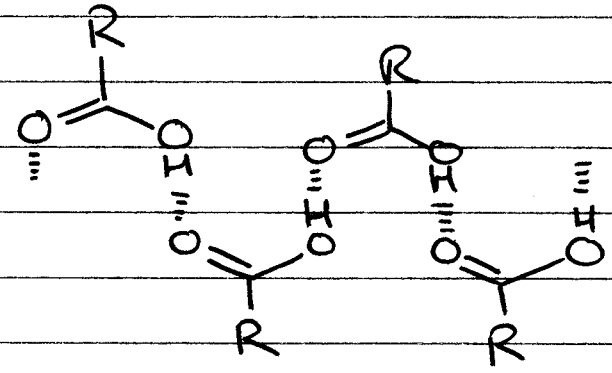


48°C

HYDROGEN BONDING

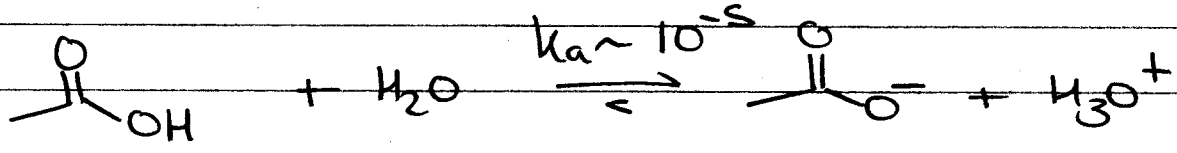


H- Bonded Dimers



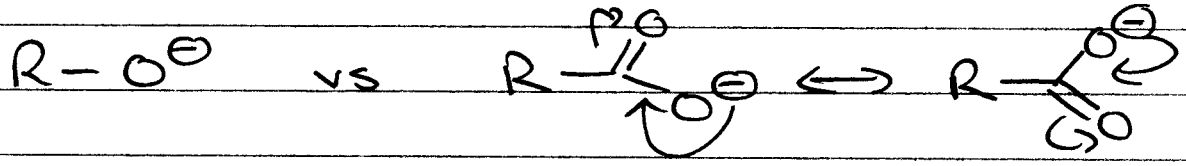
Tapes

## ACIDITY (WEAK ACIDS)




pKa ~ 5

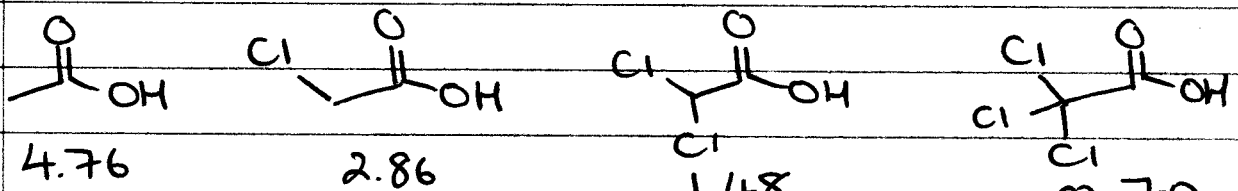
compare to alcohols R-OH pKa 16~18




RESONANCE STABILIZED

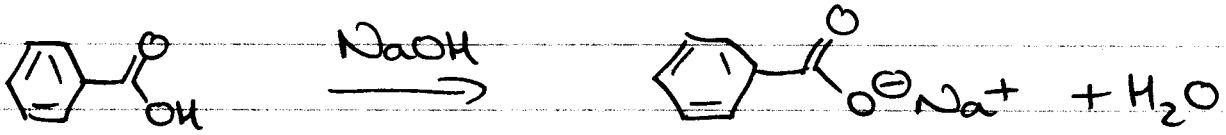
Also INDUCTIVE EFFECTS





4.76 2.86 1.48 0.70

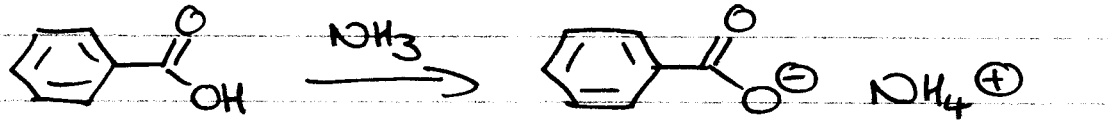
## REACTION w/ BASES




slightly water soluble

sodium benzoate (60g / 100ml)

$RCO_2H$ also reacts w/ amines & ammonia



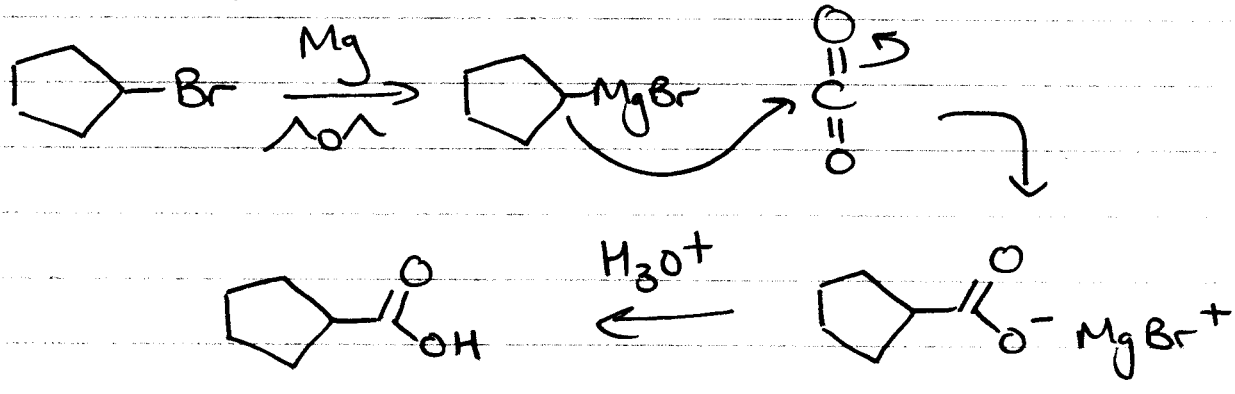

ammonium benzoate

## PREPARATION

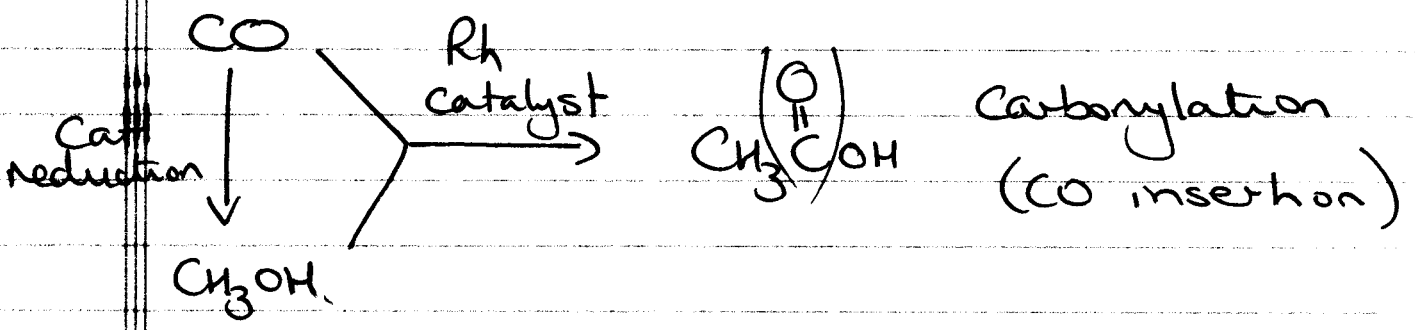
oxidation of 1° alcohols / aldehydes

$RCH_2OH \longrightarrow RCHO \longrightarrow RCO_2H$

From Grignard rxns

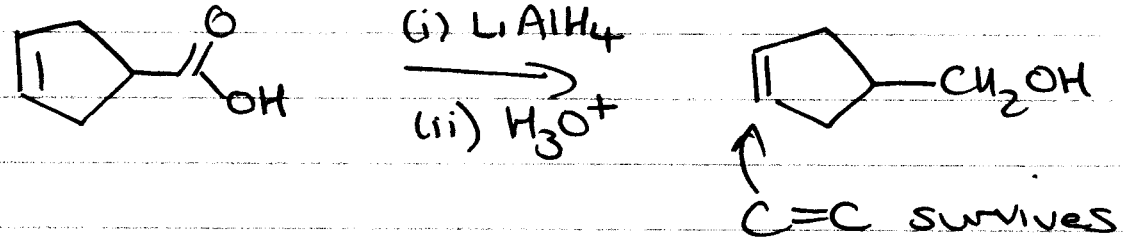


# INDUSTRIAL PREP of ACETIC ACID

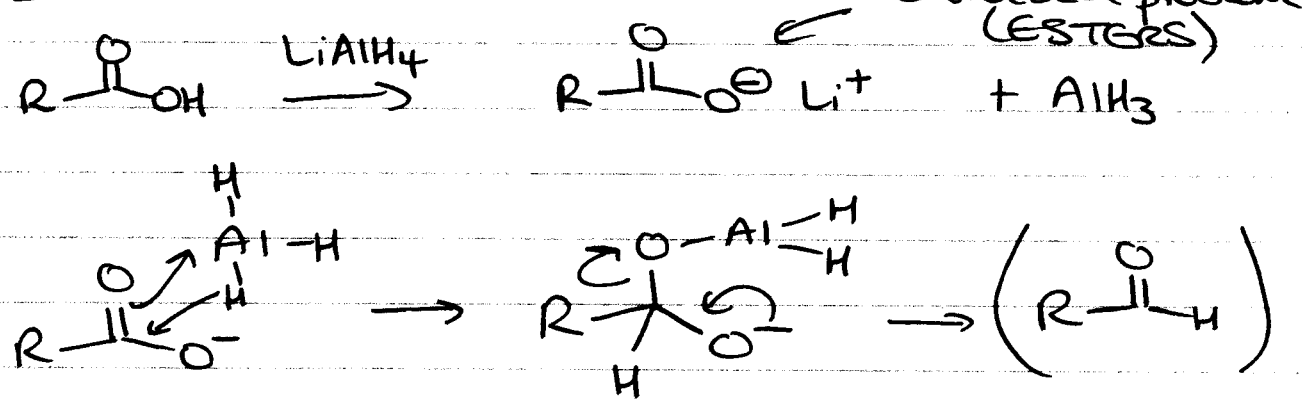


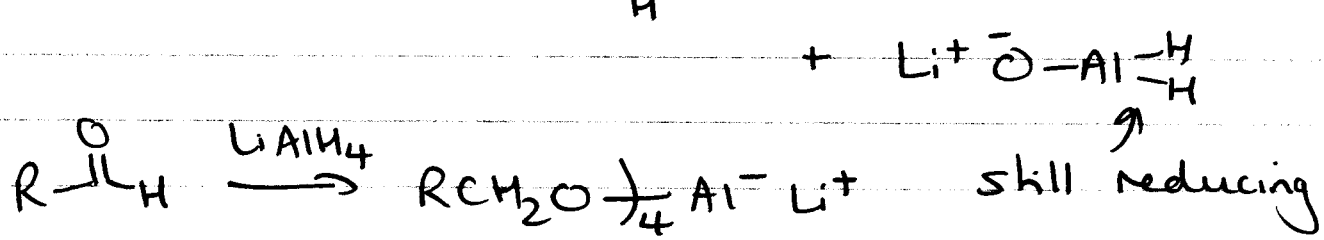

## REACTIONS

### (i) REDUCTION of $RCO_2H$

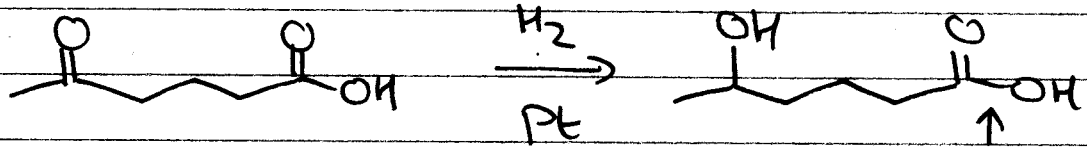



mech:

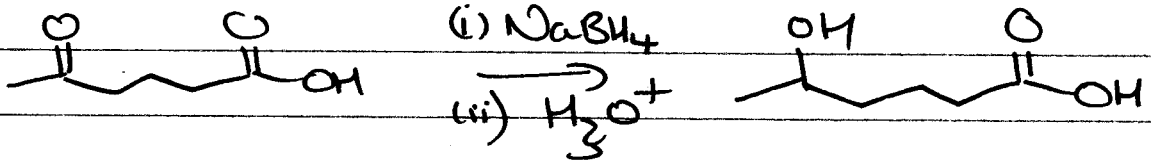


## (1) SELECTIVE REDUCTIONS

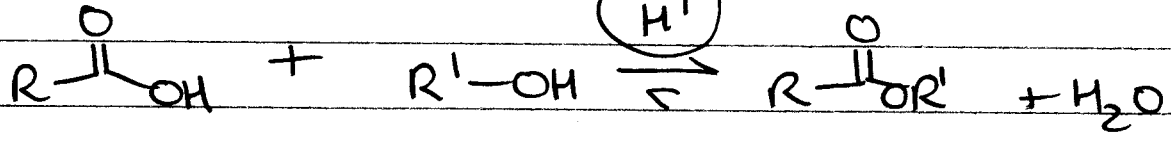


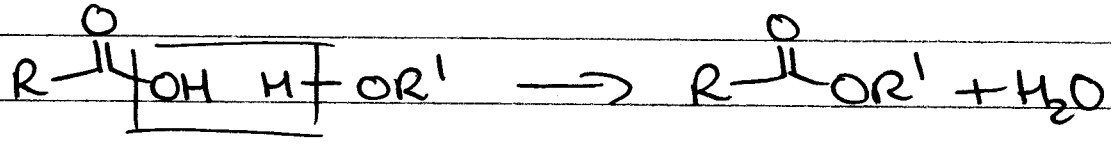

or

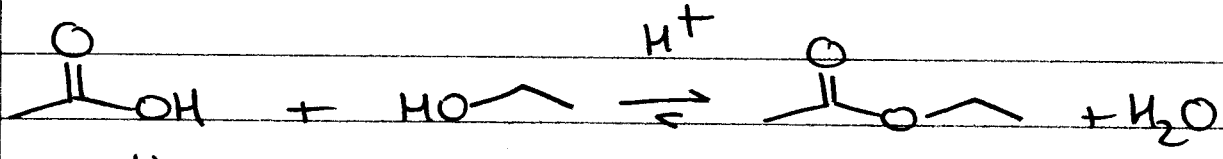



## (2) ESTERIFICATION

REVERSIBLE - FISCHER




acetic acid

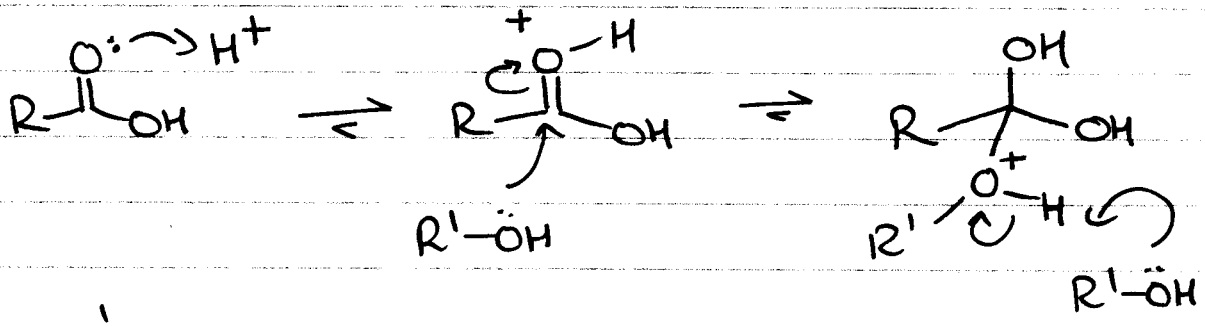
ethyl acetate

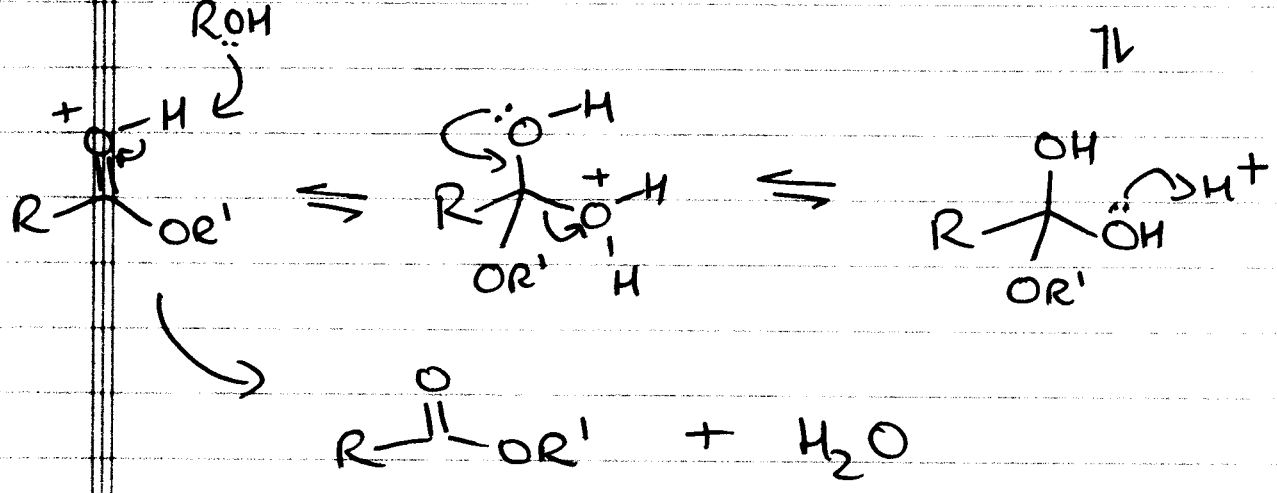
$H^+$ usually $H_2SO_4$ or HCl (g)

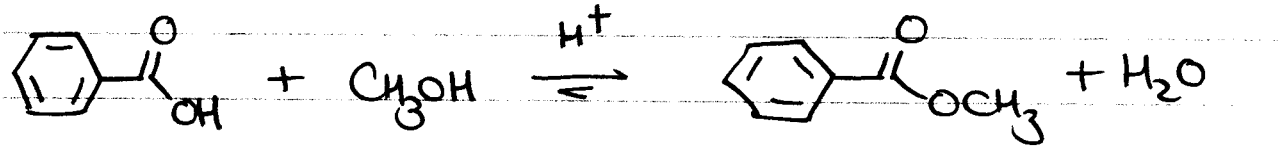
EQUILIBRIUM SHIFTED BY:

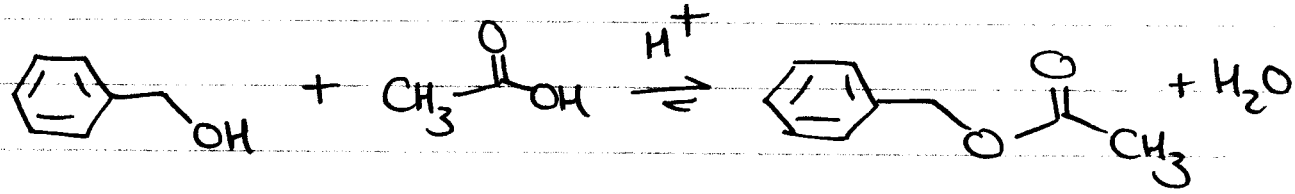
(i) Removing $H_2O$ (ii) use large xs $R'–OH$

MECHANISM
(v. important — lots of others similar)









LEC 23 

1. HMK 17.4–17.6, 17.32–17.36, * 17.38–17.41, 17.43
   18.2–6, 18.15
2. Spec answers posted over weekend

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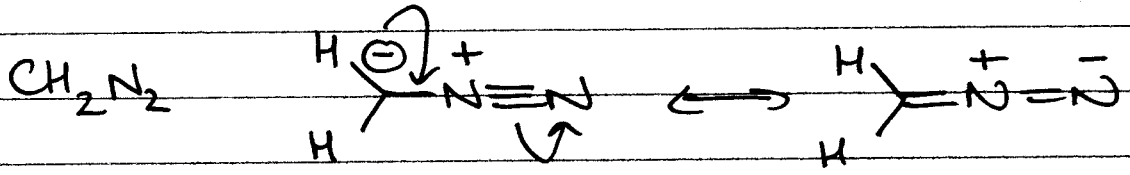
1. REDUCTION cont...
2. ESTERIFICATION
3. ACID CHLORIDES
4. DECARBOXYLATION
5. CH 18 CARBOXYLIC ACID DERIVATIVES

---

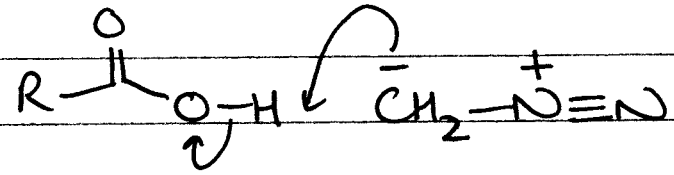
- DIAZOMETHANE (METHYL ESTERS)

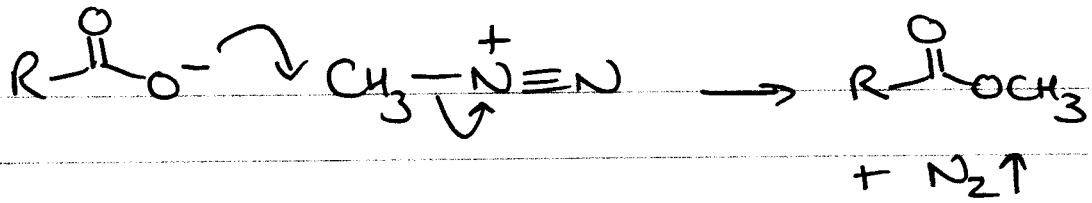
$$RCO_2H \xrightarrow[\text{ether}]{CH_2N_2} RCO_2CH_3 + N_2\uparrow$$



resonance

mech





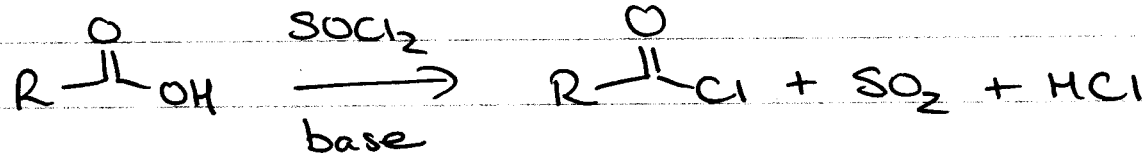
② + $N_2\uparrow$

VERY MILD CONDITIONS,
but VERY DANGEROUS, $CH_2N_2$ EXPLOSIVE

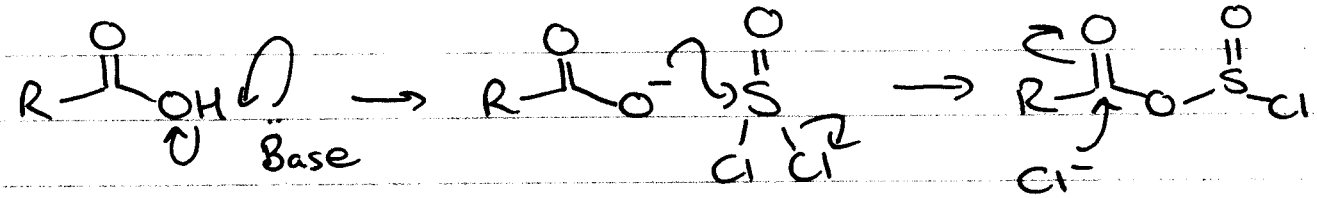
## ③ Conversion to ACID CHLORIDES

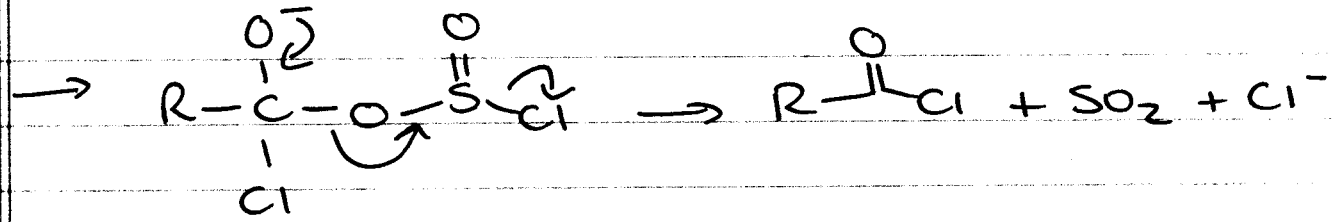
X = Cl mostly

acid halides



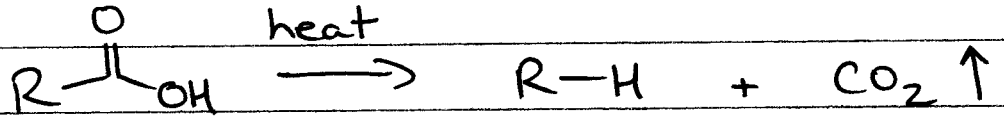
(R–OH → R–Cl)





tetrahedral intermediate

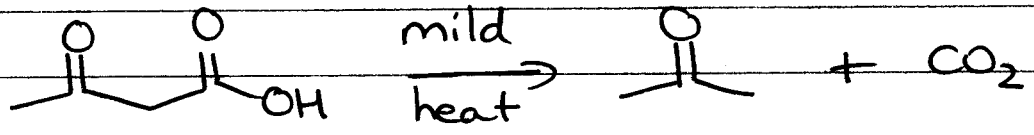
## ④ DECARBOXYLATION

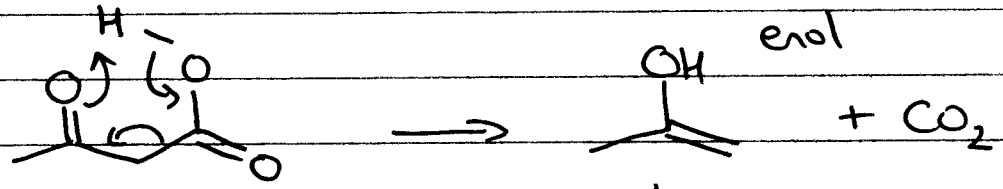



most $RCO_2H$ resistant to this process, ever melting or boiling before it happens

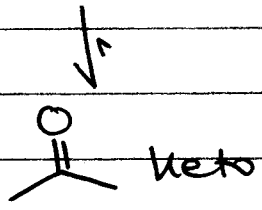
xcept:

### ① β-KETO ~~ESTERS~~ ACIDS

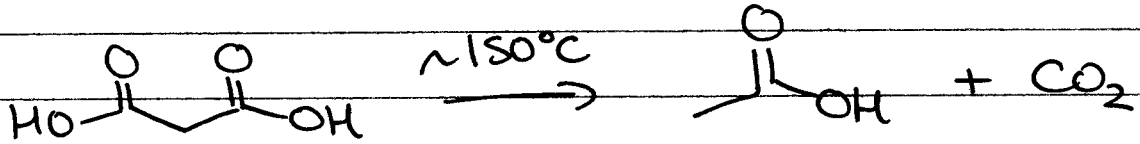



6 membered cyclic TS

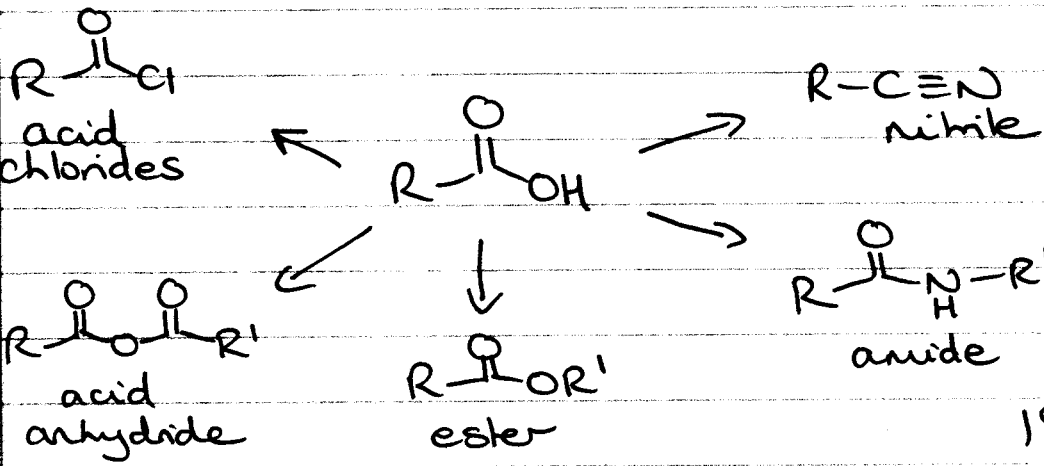



### ② MALONIC ACID




need C=O β to CARBOXYL group

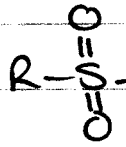
## (5) DERIVATIVES of CARBOXYLIC ACIDS

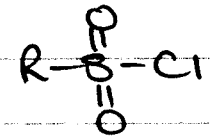



DO $1^{\circ}, 2^{\circ}, 3^{\circ}$

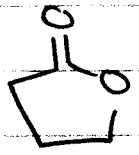
amide bond = peptide bond

a few others

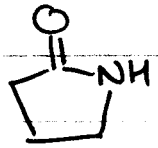
Sulfonic acids 

sulfonyl chlorides  such as TsCl (R =  )

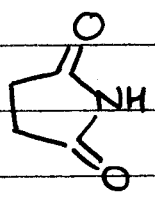
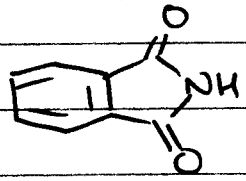
cyclic esters = LACTONES

 4 BUTANOLACTONE

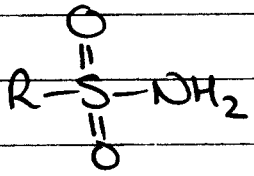
cyclic amides = LACTAMS

 4 BUTANOLACTAM

imides (two acyl groups on N — usually cyclic)

sulfonamides



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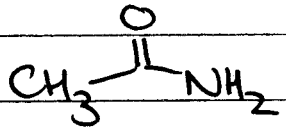
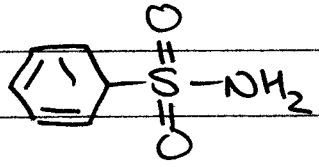
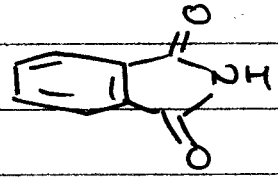
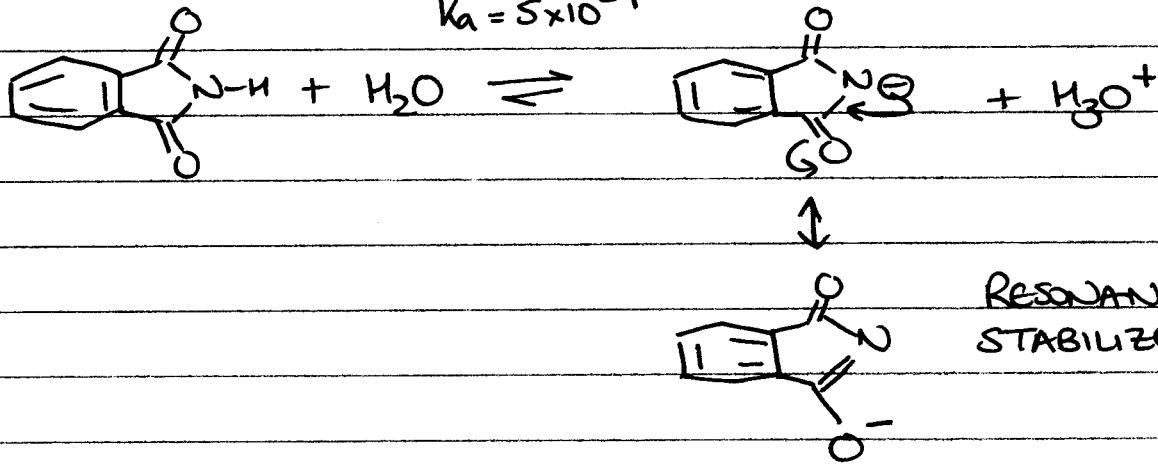
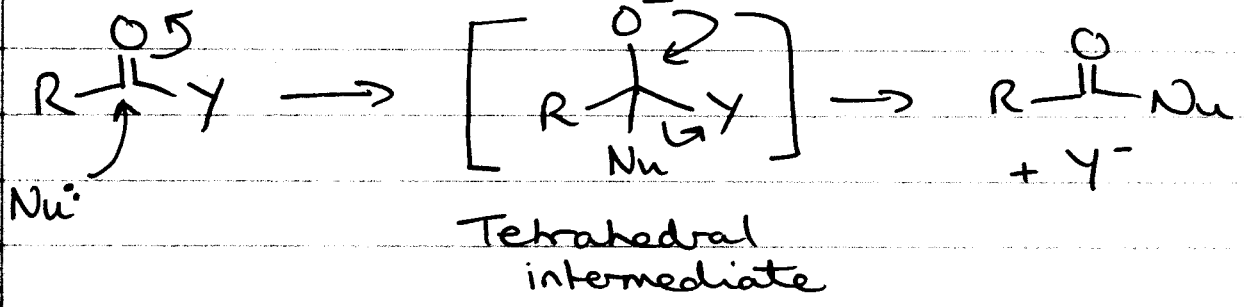
ACIDITY

pKa 15-17 ~10 ~8

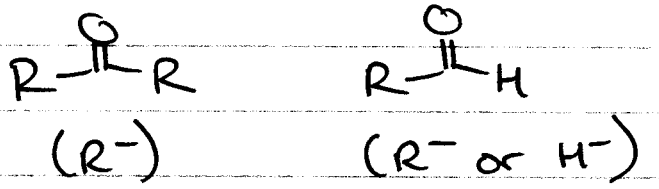


## GENERAL RXN




Nucleophilic acyl substitution

compare to:




not good leaving groups.

NO SUBSTITUTION, JUST ADDITION.

## Reactivity TRENDS

| | AMIDES | ESTERS | ANHYDRIDES | HALIDES |
|---|---|---|---|---|
| LG (Y) | $R_2N^{\ominus}$ | $RO^{\ominus}$ |  | $X^{\ominus}$ |

← INCREASING BASICITY

→ MORE STABLE ANION
INCREASED LG ABILITY
MORE REACTIVE

ACID HALIDES / ANHYDRIDES

v. reactive → not found in nature

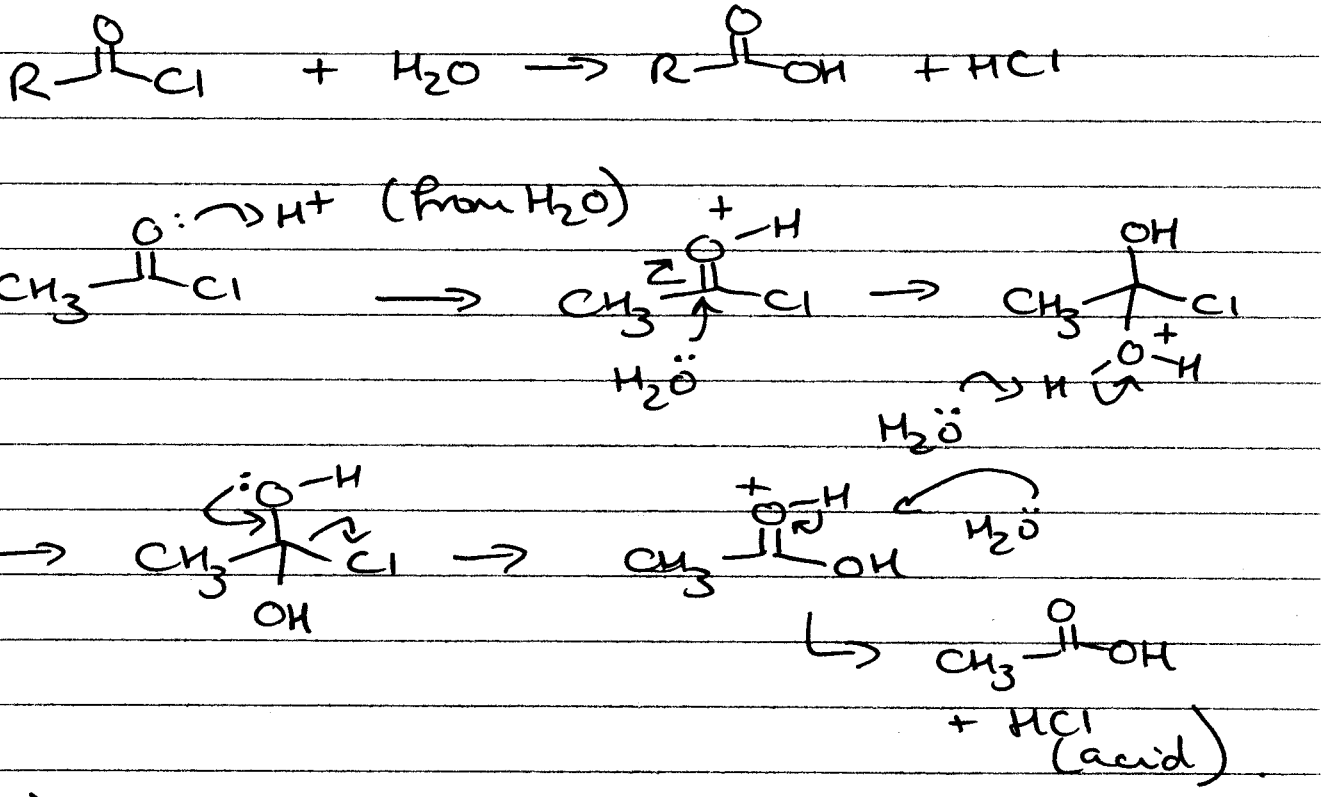
ESTERS / AMIDES

ubiquitous in Nature

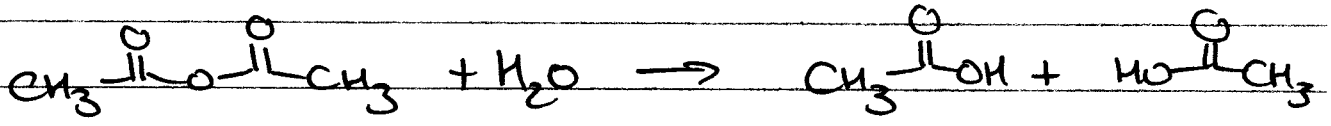
~

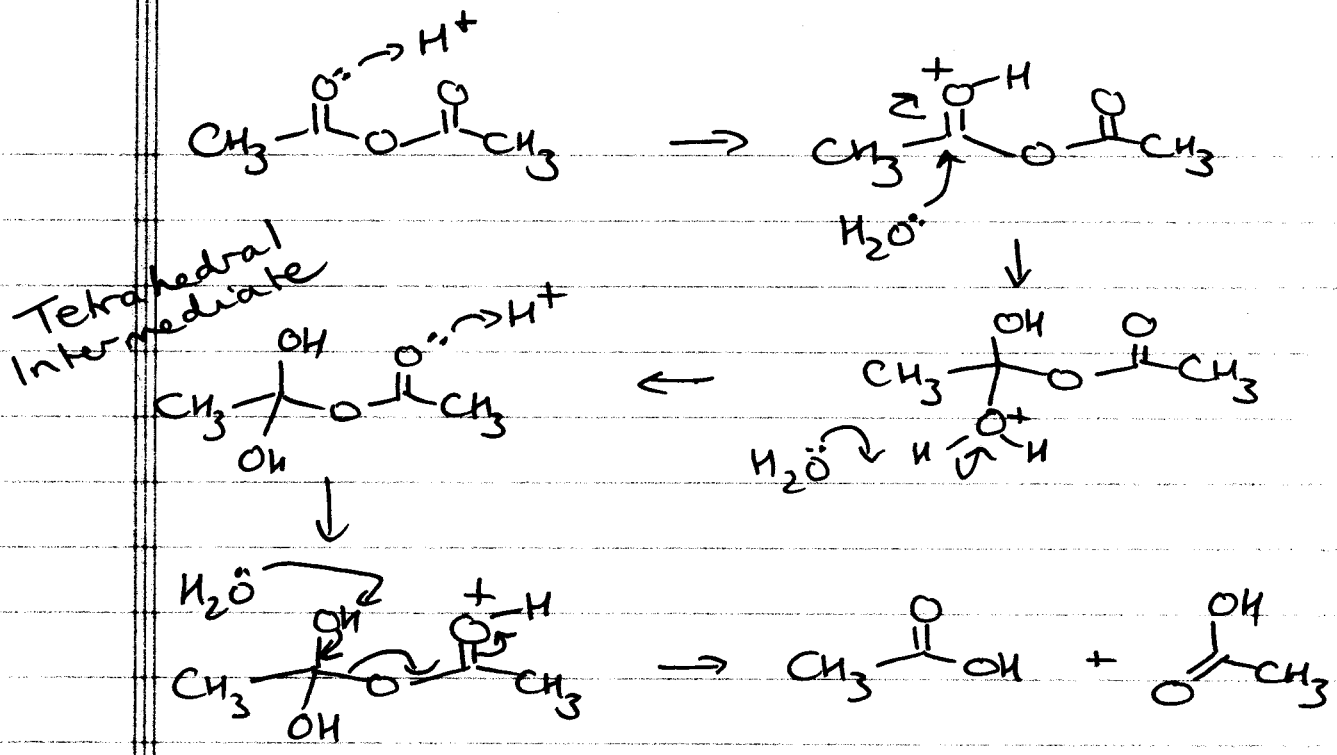
HYDROLYSIS RXNS

(i) ACID CHLORIDES




(ii) ACID ANHYDRIDES



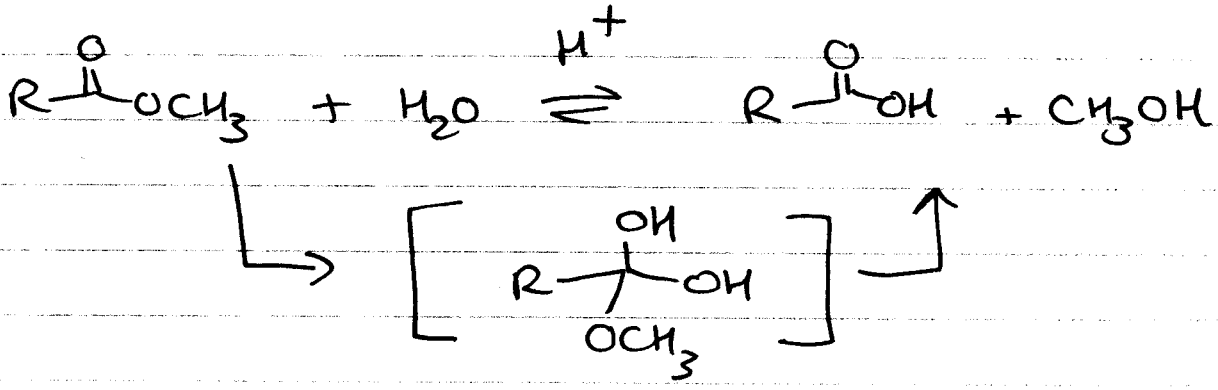



(iii) ESTERS

HYDROLYZED SLOWLY IN BOILING $H_2O$

FAST IN AQUEOUS ACID / BASE

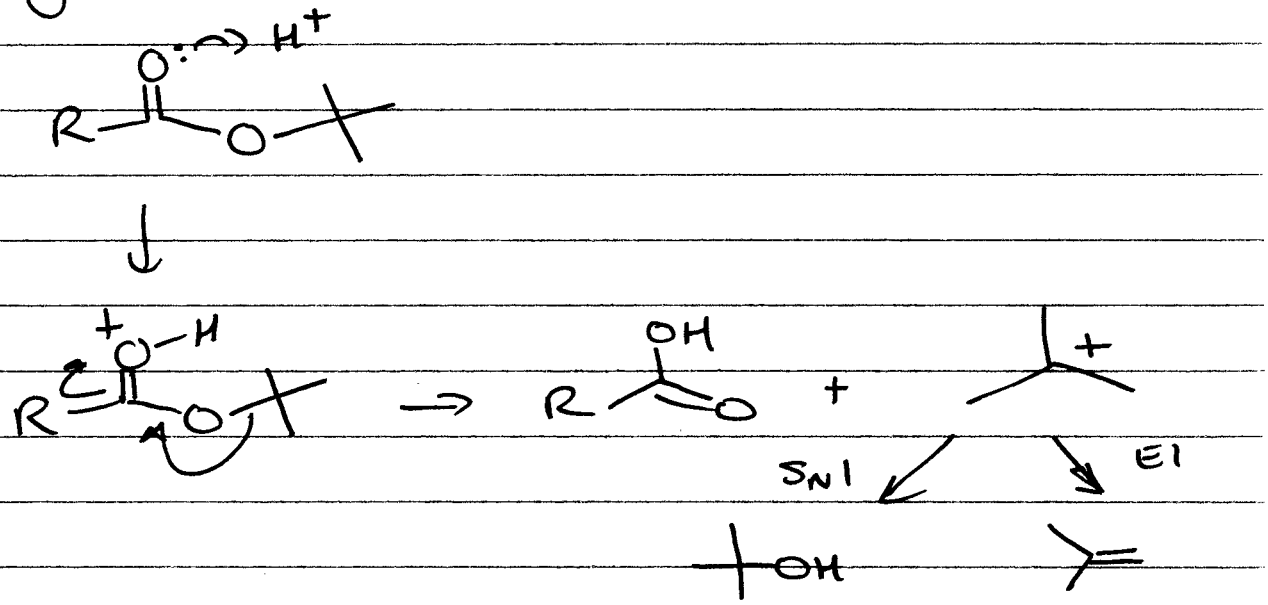
REVERSE OF FISCHER ESTERIFICATION



Tetrahedral

Alternative mechanism, if group next to O can form a stable $C^+$.

e.g. t-BUTYL ESTERS

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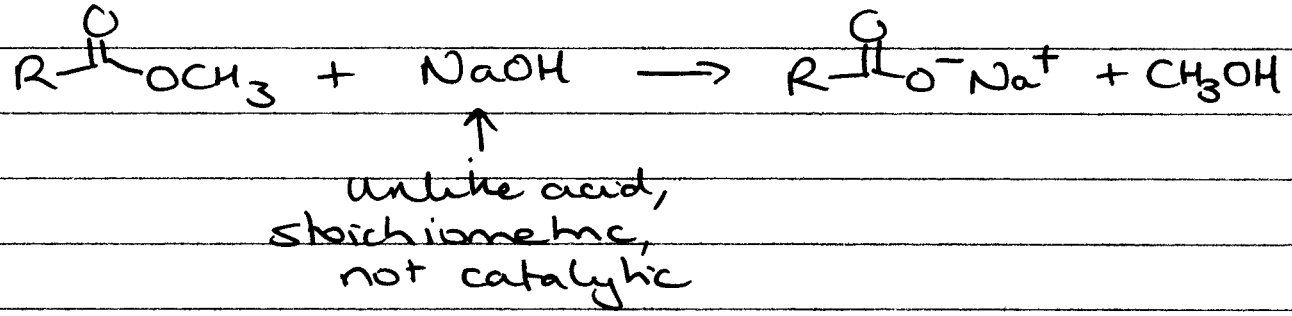
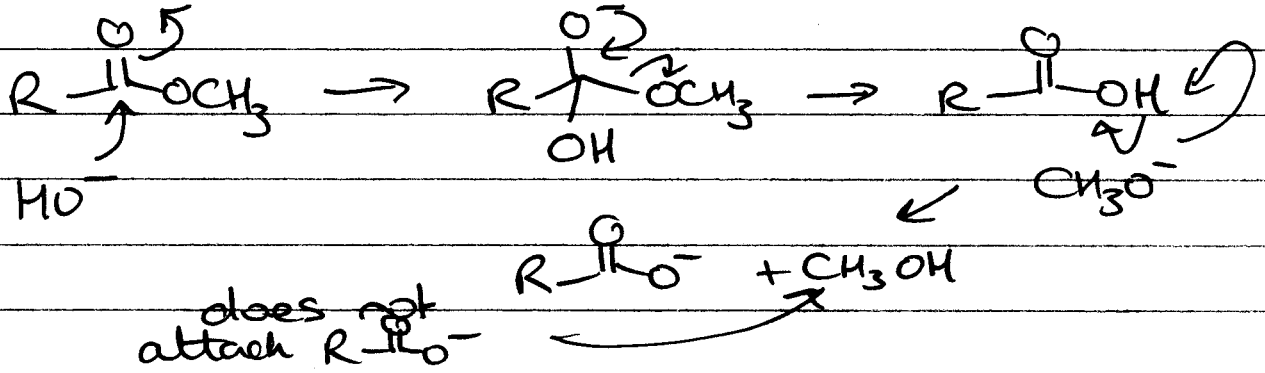
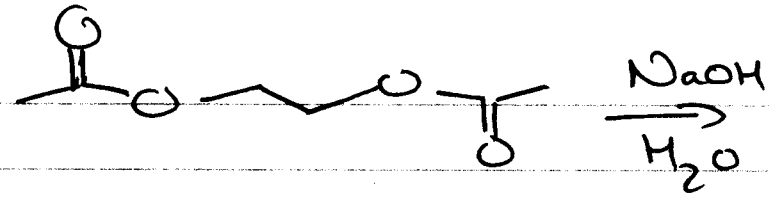
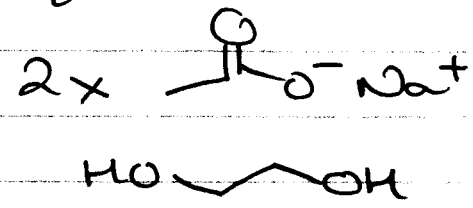
BASIC HYDROLYSIS — SAPONIFICATION



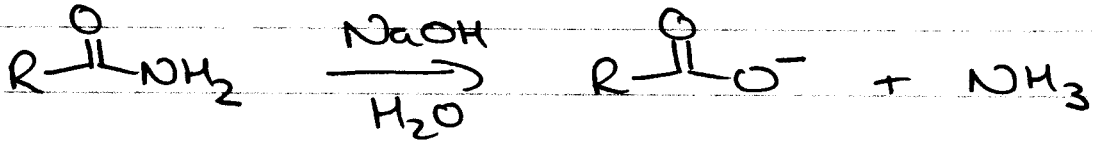





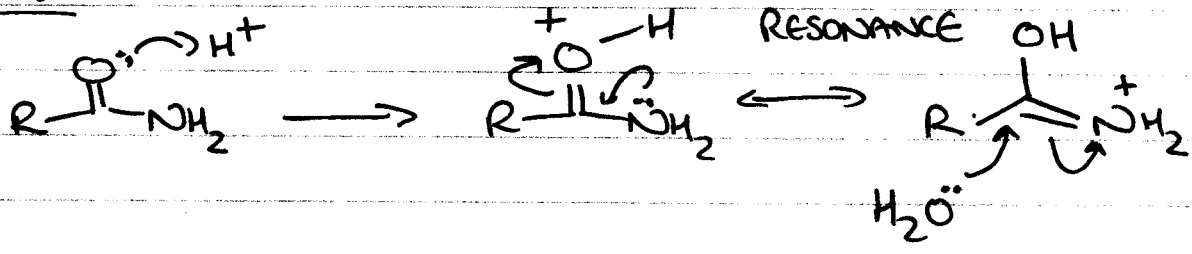



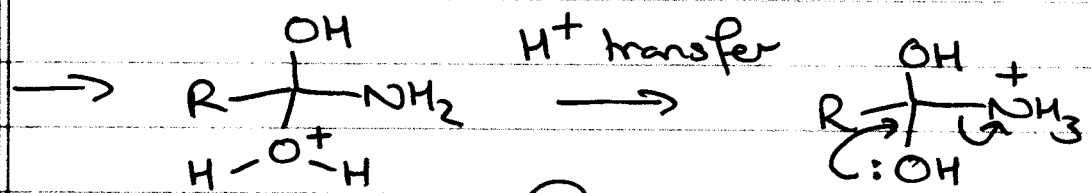

AMIDES — HARSH CONDITIONS

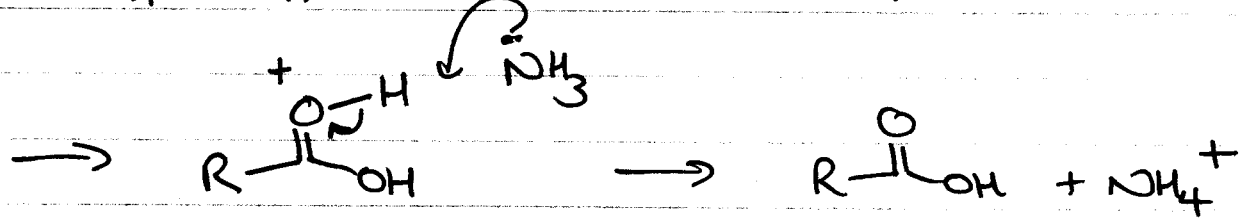
ACID or BASE — STOICHIOMETRIC


ACID



LEC ~~XX~~ (24)



(1) HMK 18.2-11, 15
(2) QUIZ on WEDS - multiple choice

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$RCO_2H$ DERIVATIVES cont

(1) ACIDITY
(2) GENERAL REACTIVITY
(3) HYDROLYSIS (RXN w/ $H_2O$)
(4) RXN w/ ALCOHOLS

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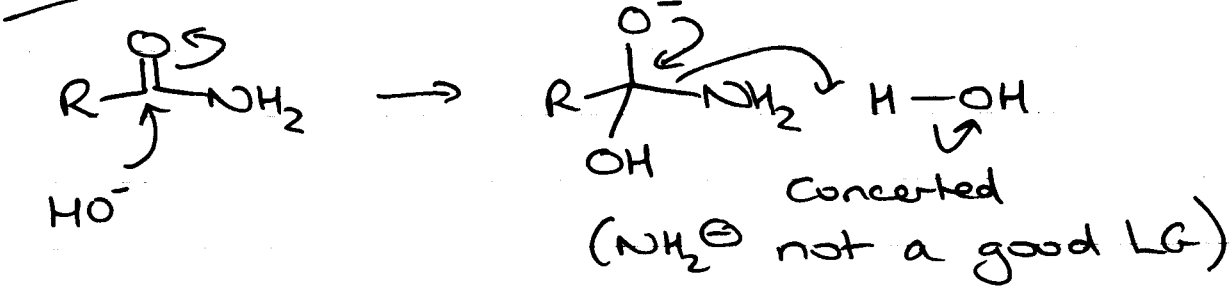
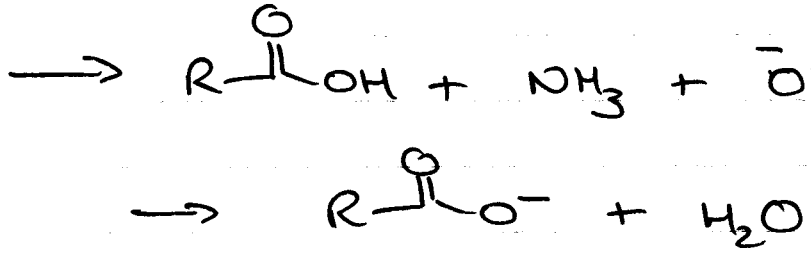
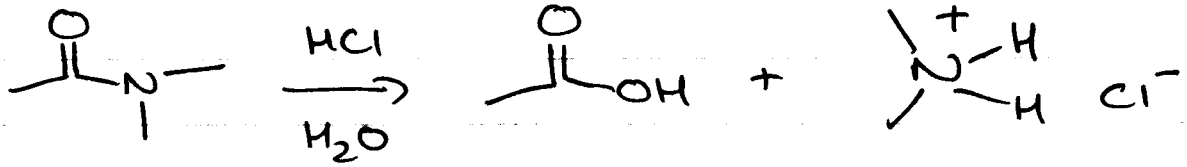
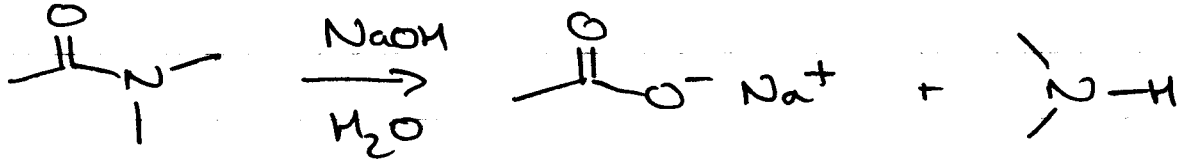
BASE



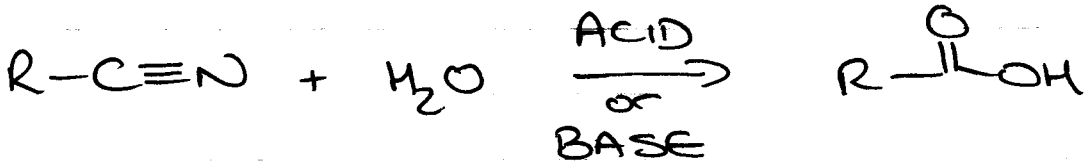




EXAMPLES



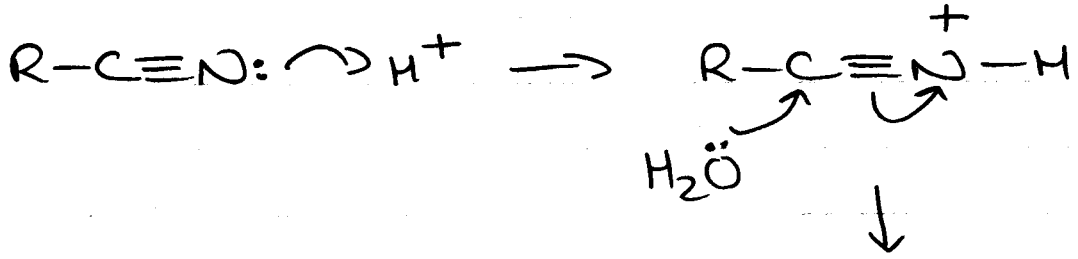



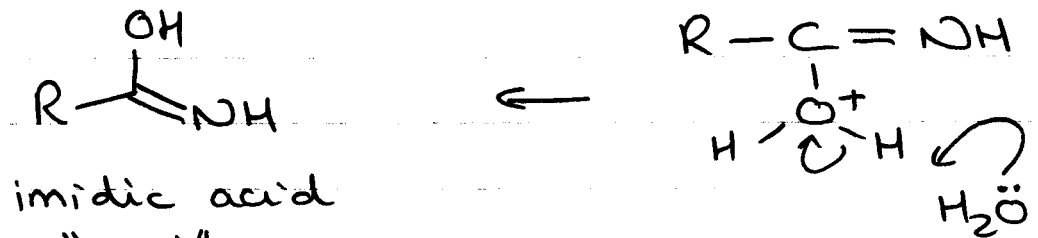

NITRILES (R–CN)

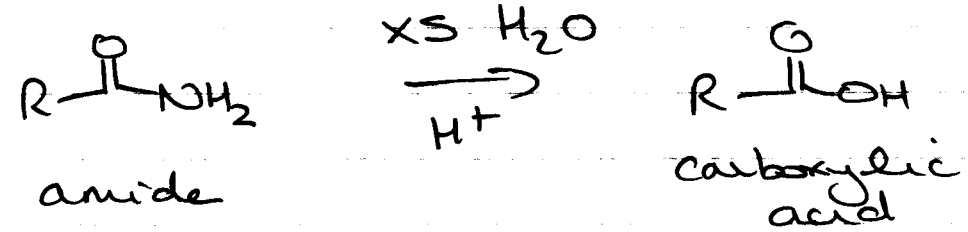



Conditions for CN hydrolysis harsher than for amides

## Acid



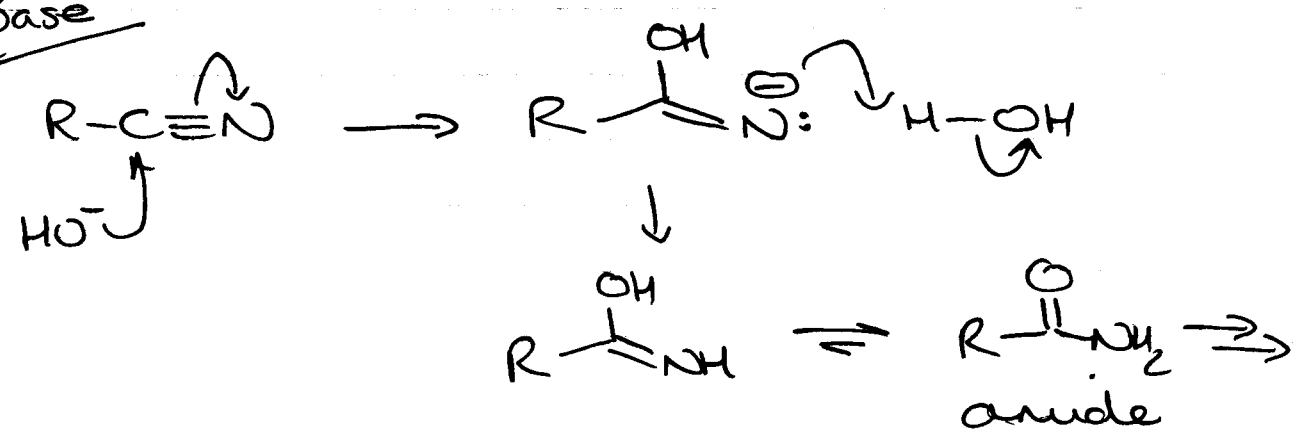


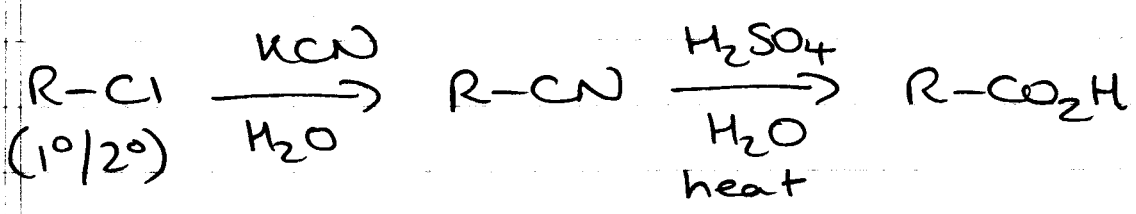

CAN ONLY STOP at AMIDE using $H_2SO_4$ (cat) and STOICHIOMETRIC $H_2O$

- not a good method for making AMIDES

## Base



useful for synthesis 

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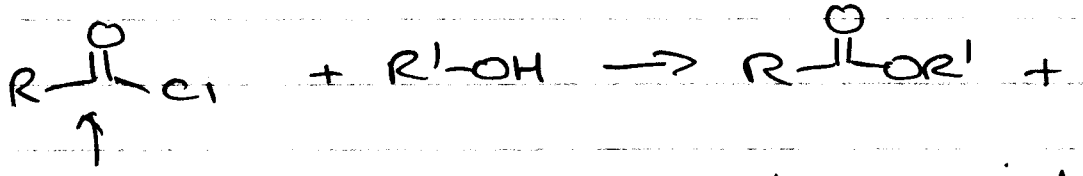
## (4) RXNS W/ ALCOHOLS

### (i) ACID CHLORIDES

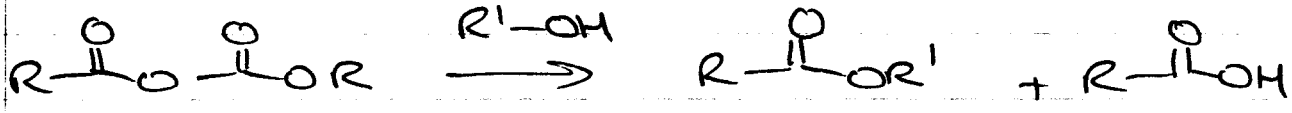



so reactive, no catalyst required

(If ester or alcohol is acid sensitive, a 3° amine such as $Et_3N$ or py is added to neutralize the acid produced)

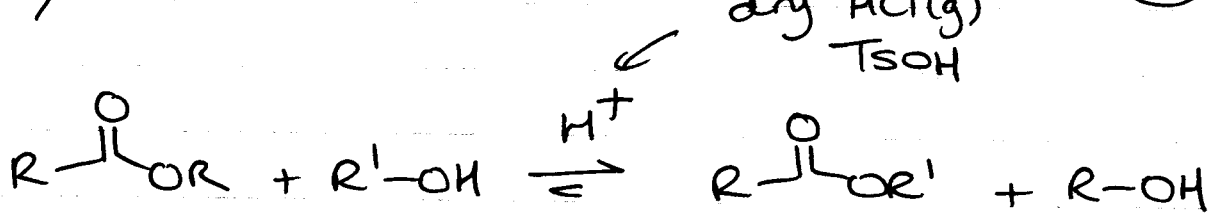
Mechanism like H–OH, but R'–OH

### (ii) ACID ANHYDRIDES

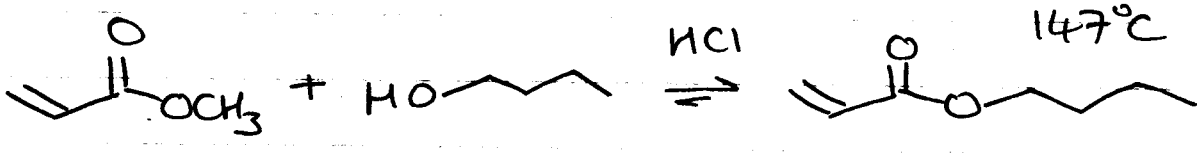



catalyzed by $H^+$ or 3° AMINES
again mechanism like H–OH, but R'–OH

## (iii) ESTERS




Transesterification




81°C 117°C

$CH_3OH$ 65°C

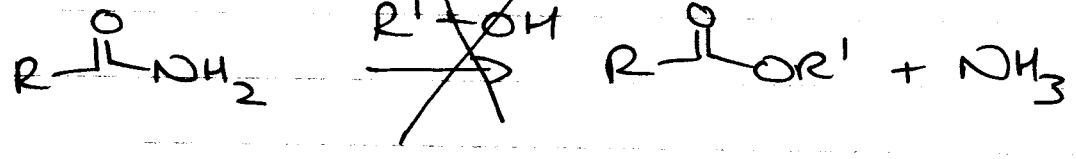
Equilibrium

BOIL OFF $CH_3OH$ ⟶

⟵ LARGE XS of $CH_3OH$

## (iv) AMIDES

DO NOT REACT w/ R'-OH



STAMPS / OFFICE HOURS / HANDOUT / QUIZ 3

Lec ~~XX~~ (25) 

(1) There will be CLASS on FRIDAY
(2) Last day to hand in EXTRA CREDIT FRI
(3) EVALUATIONS on FRIDAY
(4) EXTRA OFFICE HOURS – MONDAY
(5) HMK 18.12, 18.20 – 18.53

---

(1) HYDROLYSIS RXNS
(2) ALCOHOLYSIS
(3) RXN w/ AMINES
(4) ORGANOMETALLICS
(5) REDUCTION

---

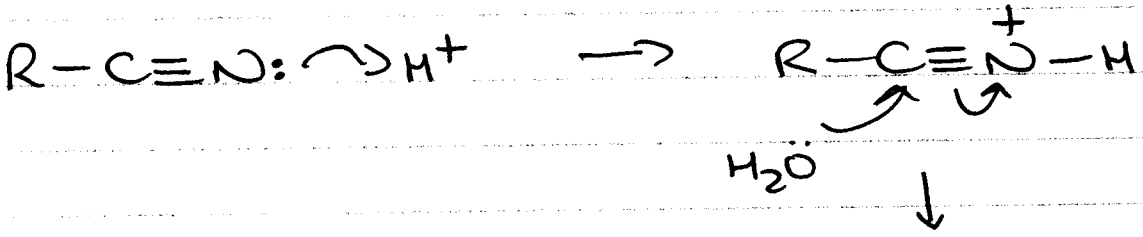
HYDROLYSIS cont

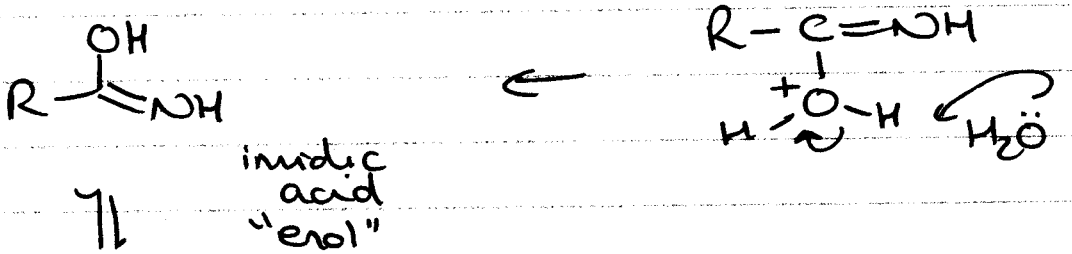
NITRILES R–CN

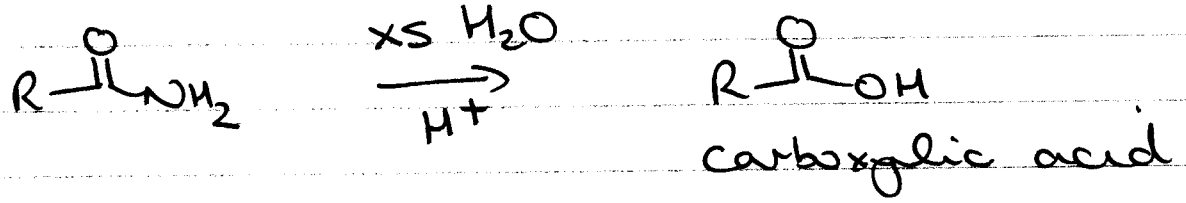
$$R\text{–}C{\equiv}N + H_2O \xrightarrow[\text{BASE}]{\text{ACID or}} R\text{–}\underset{\underset{\Large O}{\Vert}}{C}\text{–}OH$$

–CN hydrolysis harsher conditions than for amide hydrolysis

## ACID

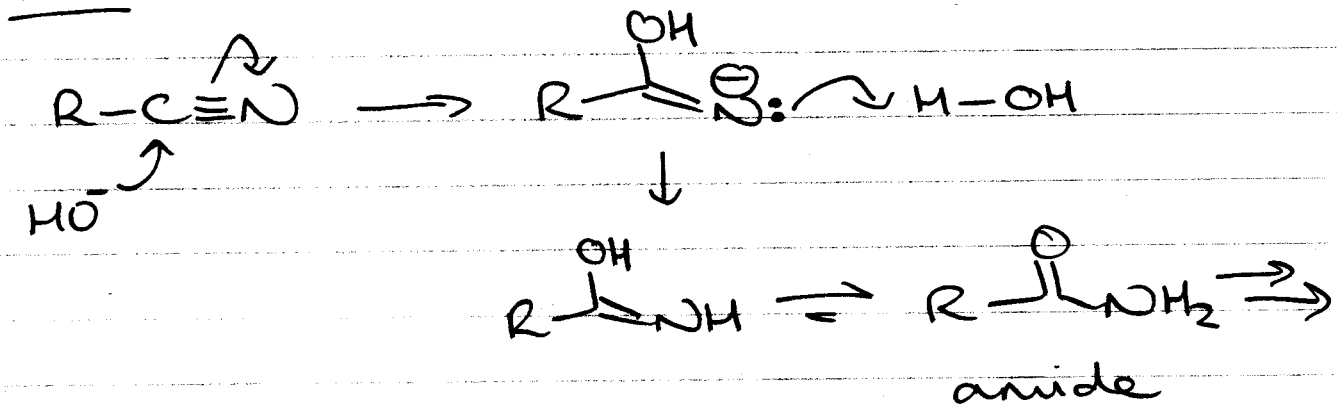





- CAN ONLY STOP at AMIDE using $H_2SO_4$ (cat) and STOICHIOMETRIC $H_2O$
- not a good method for making amides

## BASE



- useful for synthesis

$$R\text{-}Cl \xrightarrow[H_2O]{KCN} R\text{-}CN \xrightarrow[H_2O,\ heat]{H_2SO_4} RCO_2H$$

1°/2°

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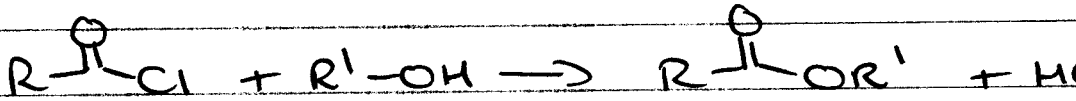
## (2) RXNS w/ ALCOHOLS

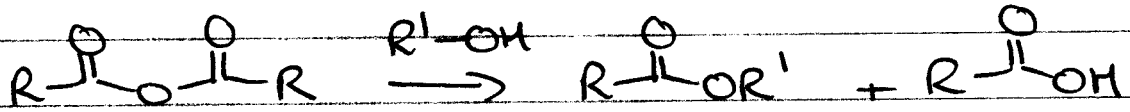
same as for H–OH, but use R–OH

### (i) ACID CHLORIDES



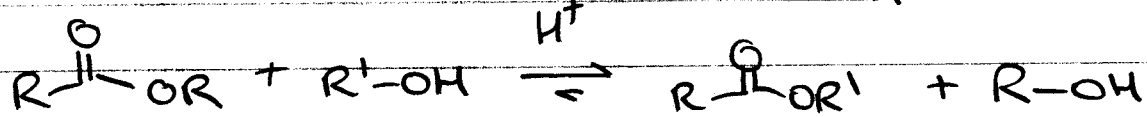
(if ester/alcohol $H^+$ sensitive, use a 3° base to mop up HCl)

### (ii) ANHYDRIDES

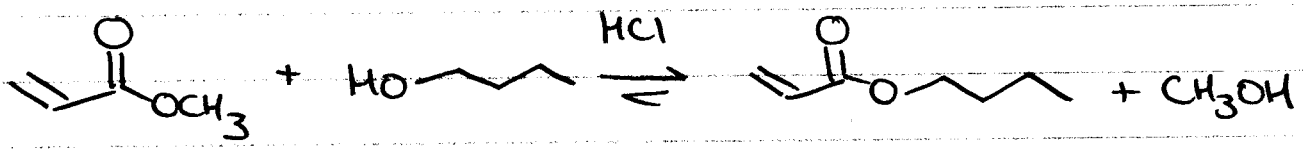


catalyzed by $H^+$ or 3° AMINES

### (iii) ESTERS



Transesterification




81°C 117°C 147°C 65°C

equilibrium

BOIL OFF $CH_3OH$ ⟶
⟵ LARGE xs OF $CH_3OH$

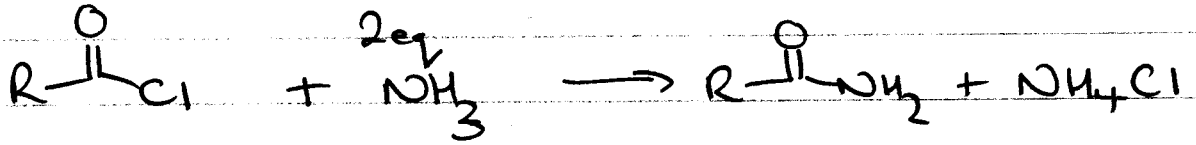
(iv) AMIDES

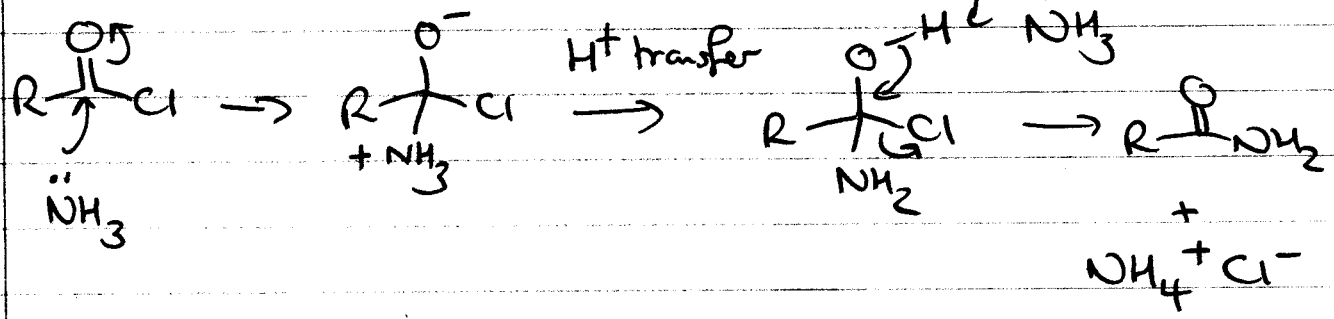
DO NOT REACT w/ R'-OH

~~~~

(3) RXNS w/ $NH_3$ or AMINES

(i) acid chlorides

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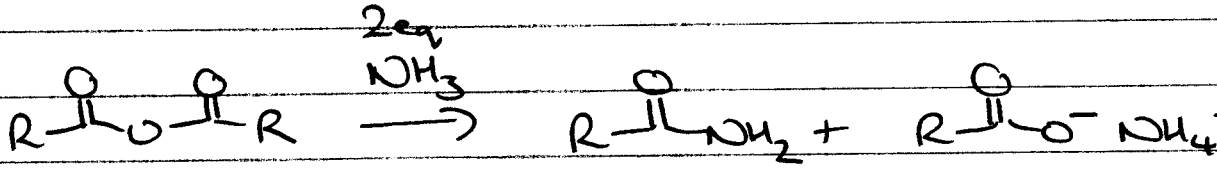
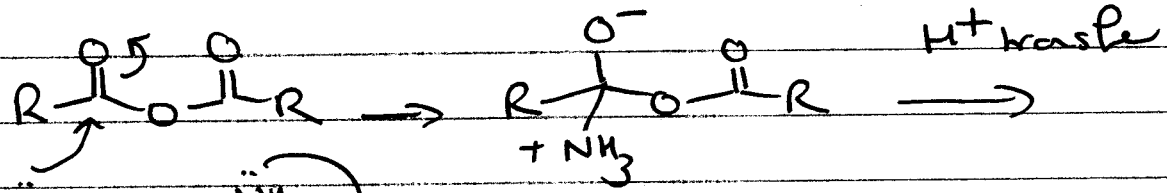
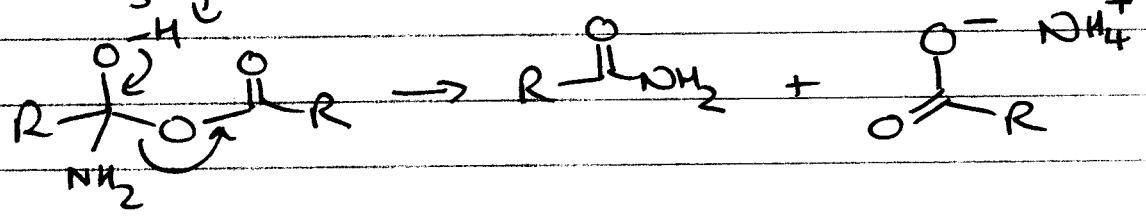
Sometimes add a 3° amine to mop up acid e.g.  or $Et_3N$

(ii) ACID ANHYDRIDES



(iii) ESTERS
(not as reactive as RCOCl or anhydrides)

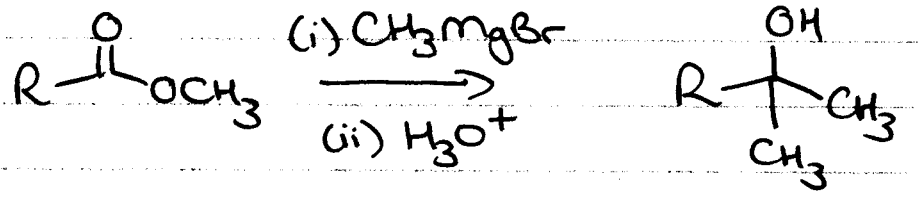
Work out mechanism for HMK

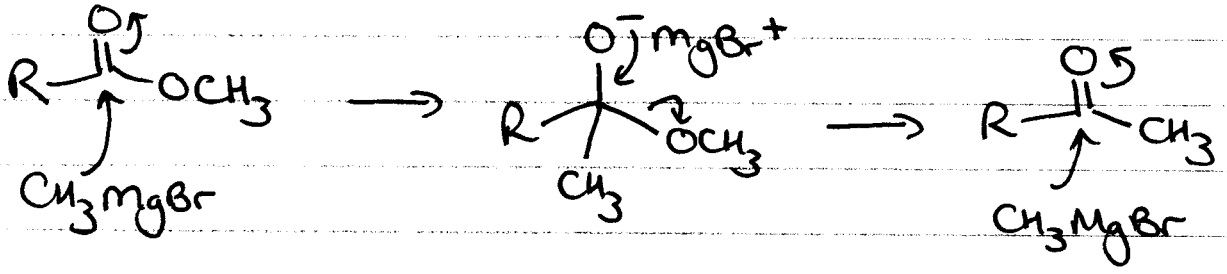
(iv) AMIDES

-do not react w/ AMINES

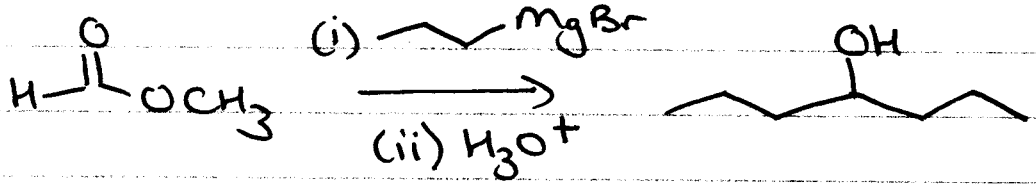
## ④ ORGANOMETALLICS

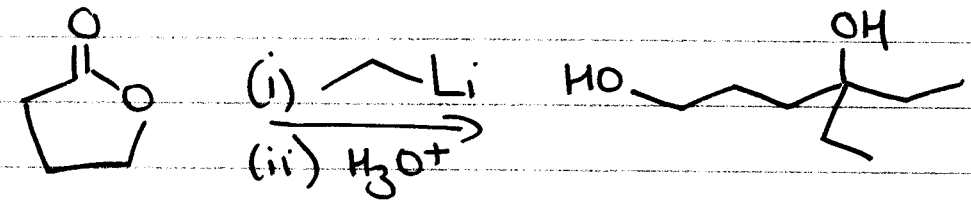
### – GRIGNARDS & ORGANOLITHIUMS



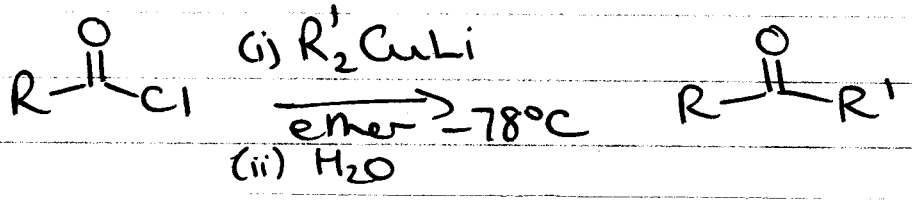




KETONE more REACTIVE THAN ESTER



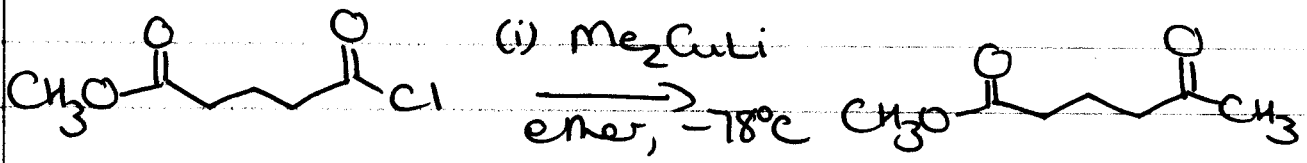




### – GILMAN + ACID CHLORIDE



At −78°C GILMAN only reacts w/  ⑦

no rxn w/ aldehyde, ketone, esters, amides, anhydrides, nitriles.

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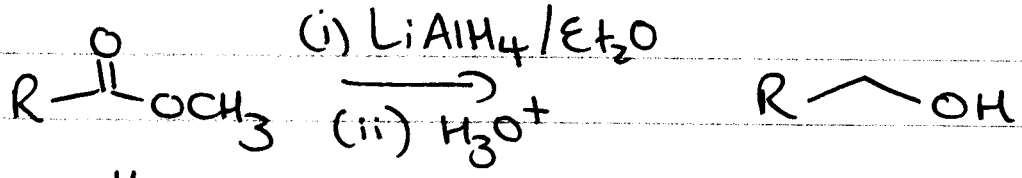
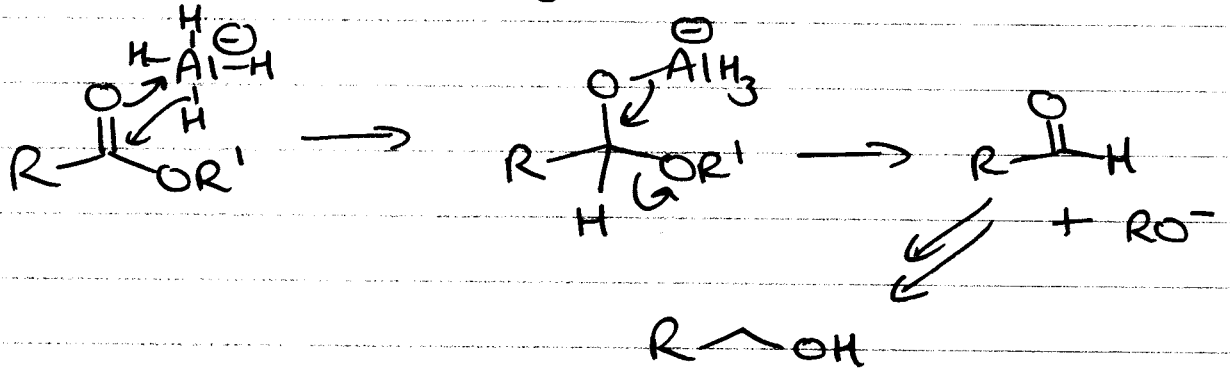
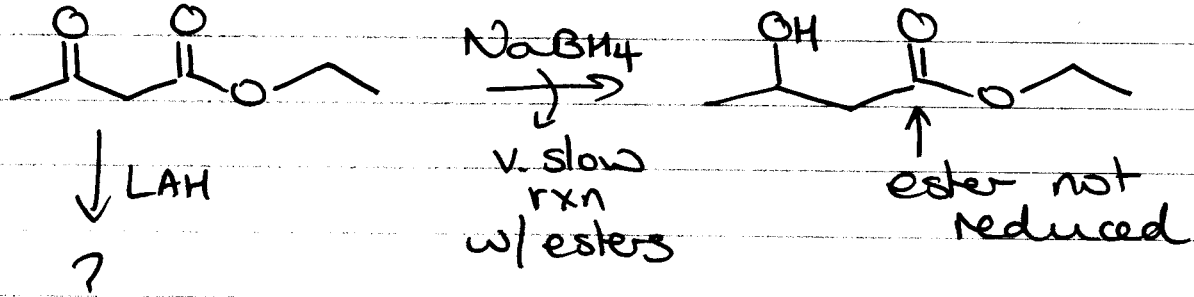
## ⑤ REDUCTION

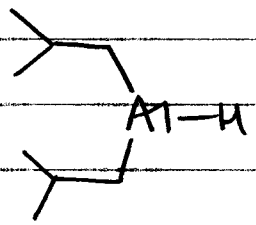


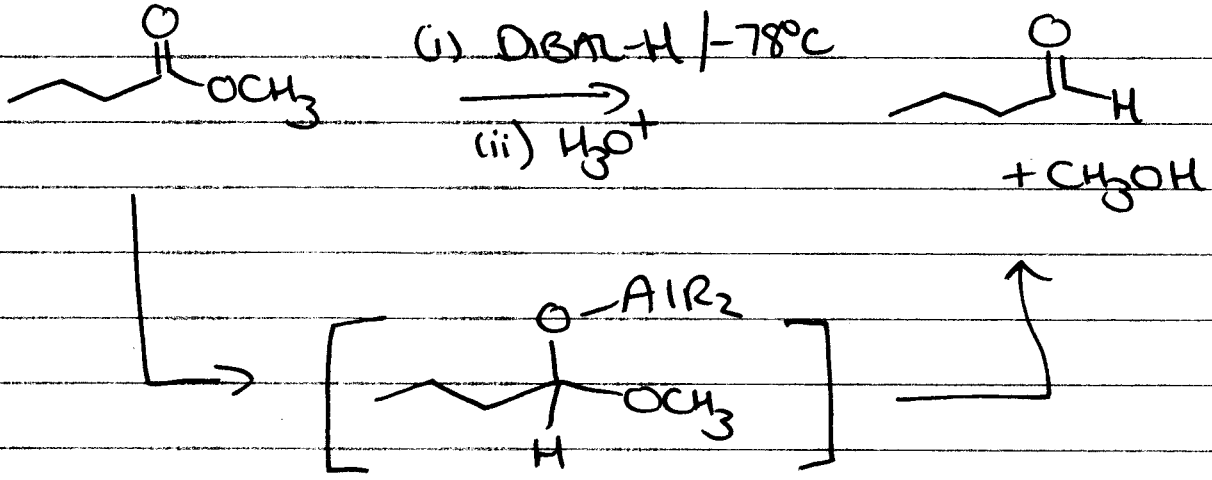




WORK OUT FR HMK

DIBAL-H



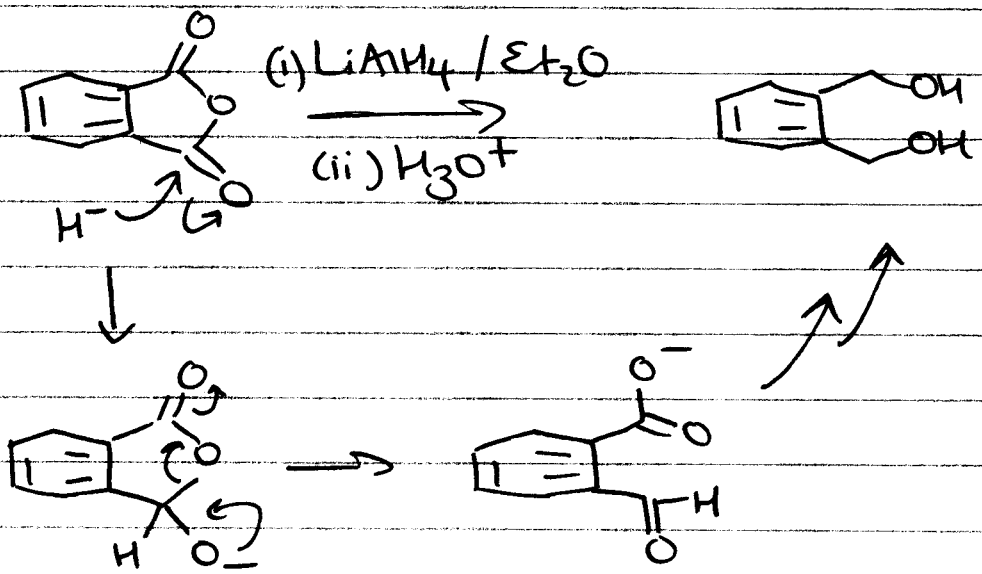
DIISOBUTYLALUMINUM HYDRIDE

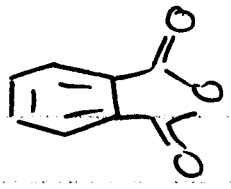



DOES NOT ELIMINATE AT LOW TEMP

at RT, 1° alcohol is formed (like LAH)

— ANHYDRIDES

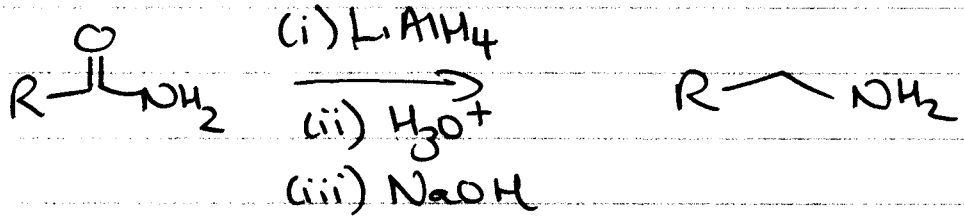


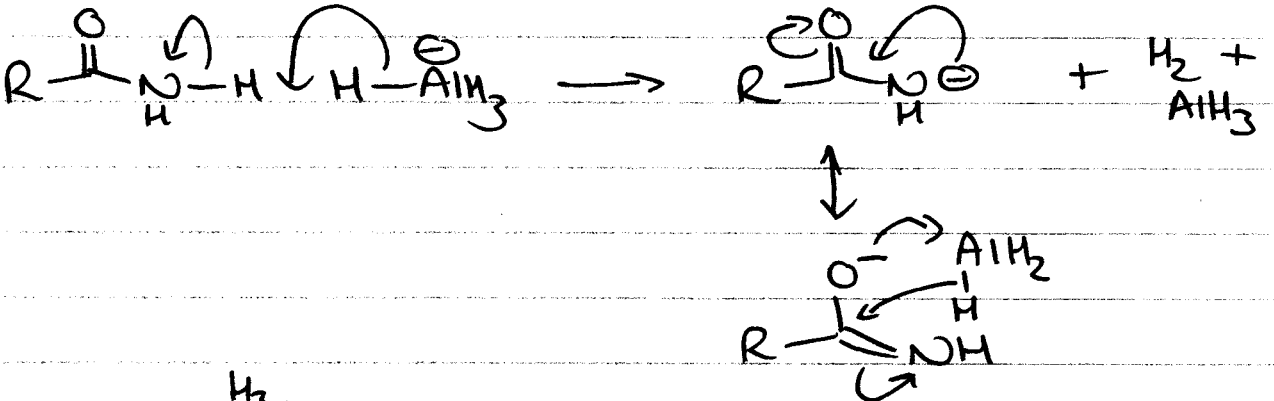


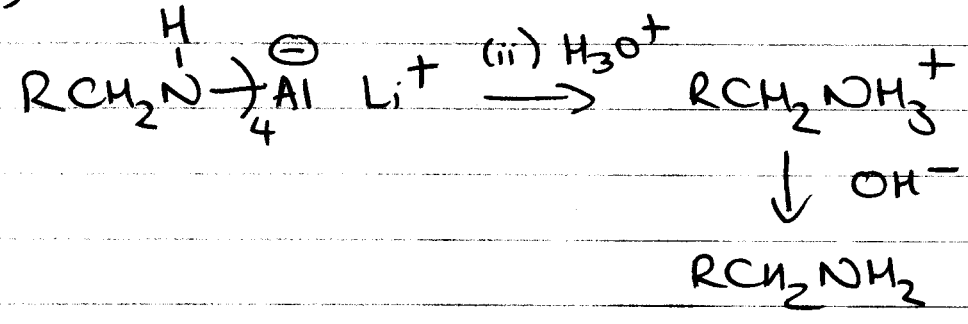

?



## AMIDES



## – NITRILES

$$R-C\equiv N \xrightarrow[\text{(ii) } H_3O^+ \\ \text{(iii) } OH^-]{\text{(i) LAH}} R-CH_2NH_2$$

only 1° amines

don't worry about mechanism

$$R-C\equiv N \xrightarrow[\text{Raney Ni}]{H_2} RCH_2NH_2$$

$$\left[R-\underset{H}{C}=NH\right]$$

imine

$$R-C\equiv N \xrightarrow[\text{hexane, } 0^\circ C \\ \text{(ii) } H_3O^+]{\text{(i) DIBAL-H}} R-\overset{O}{\overset{\|}{C}}-H \; ?$$

(i) $R-\underset{H}{C}=NH$ (ii)

imine

– Read Section 18.12 on Hofmann Rearrangement