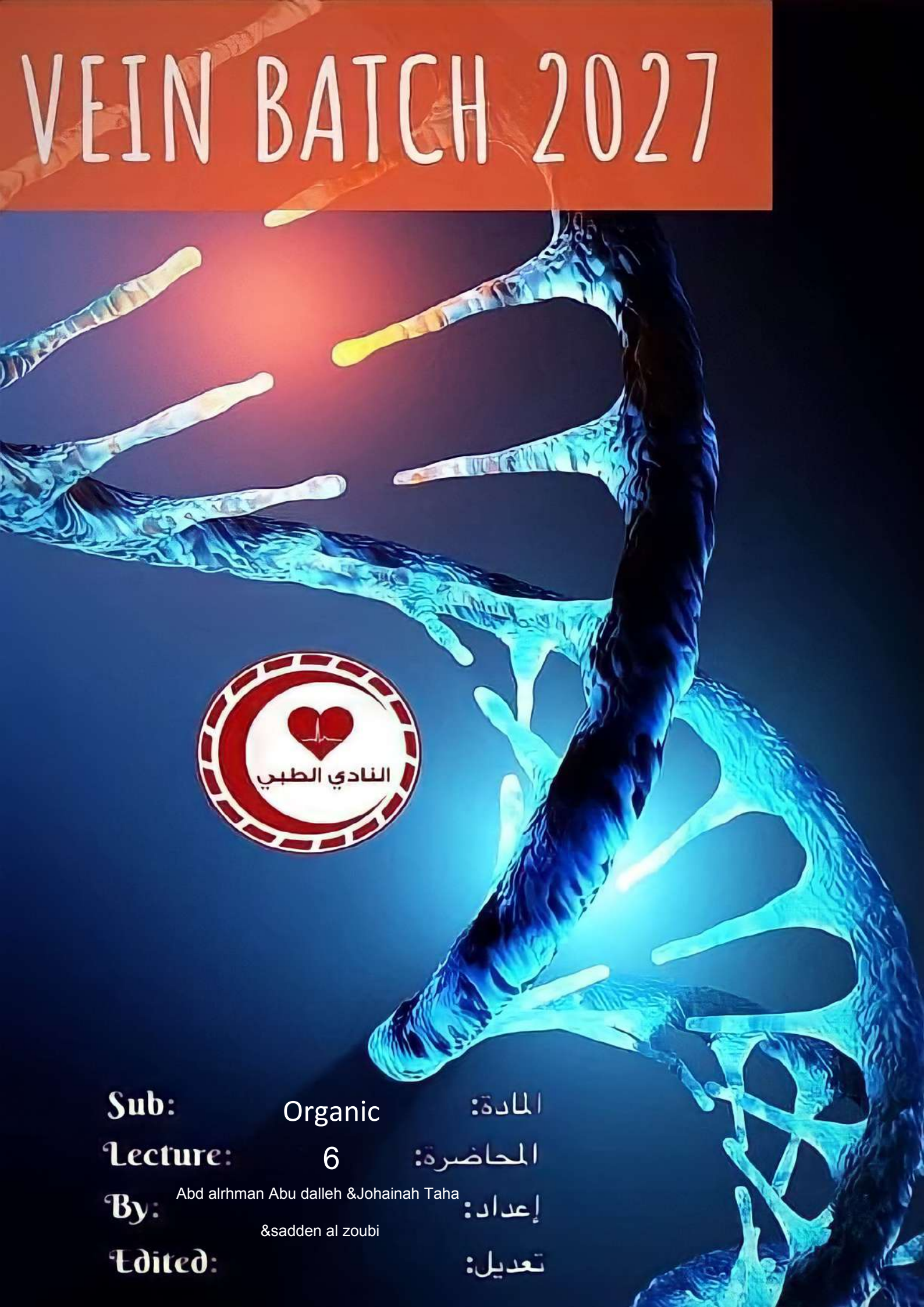
VEIN BATCH 2027



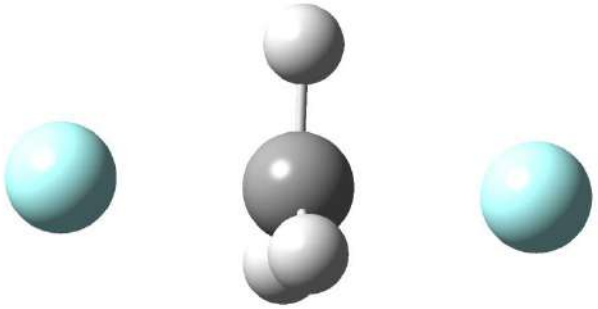
النادي الطبي

Sub: Organic المادة:

Lecture: 6 المحاضرة:

By: Abd alrhman Abu dalleh &Johainah Taha &sadden al zoubi إعداد:

Edited: تعديل:



Part 2

Chapter 6: Nucleophilic Substitution and Elimination Reactions

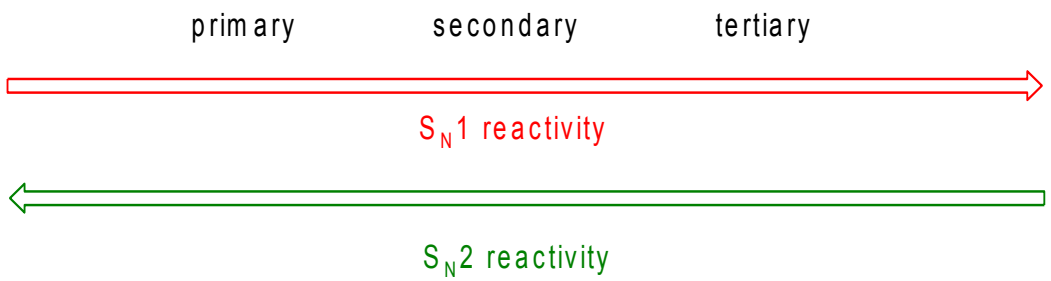
Done by :
Johainah Taha
Abed-Al-Rahman Abu Dalleh
Sadeen Al-Zoubi

ملاحظة : تم إعادة ترتيب بعض السلايدات بناءً على شرح دكتور إياد
بالتوفيق يارب 🙏🤍

Alkyle halide

S_N1 vs. S_N2: Nature of Substrate

The substrate itself has an effect on the mechanism. S_N1 requires an intermediate carbocation, while S_N2 requires a backside attack of the nucleophile (steric effects), i.e.



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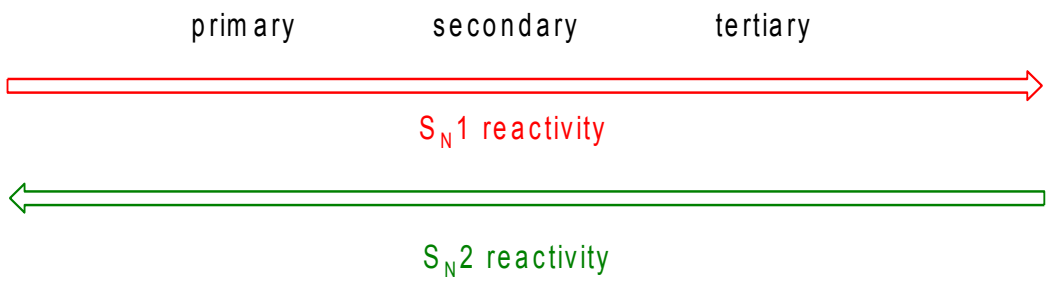
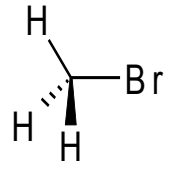


S_N1 vs. S_N2: Nature of Substrate

Reactivity of Alkyl bromide to S_N1 mechanism:



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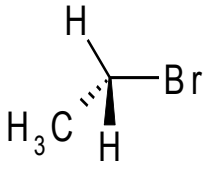
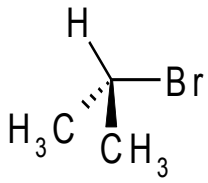


2



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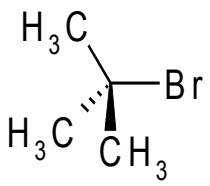
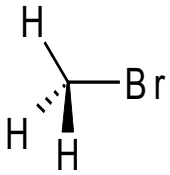


100,000,000

Reactivity of Alkyl bromide to S_N2 mechanism:



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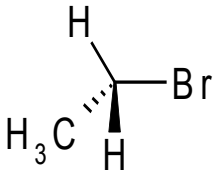

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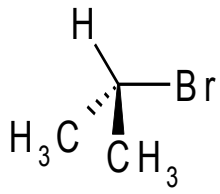

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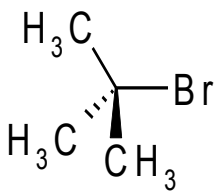


too small to measure

Record 14
2:00

S_N1 vs. S_N2: Solvent Effects

The solvent can effect the rate of formation and stability of charged species. In general two types of solvents are used:

- Polar protic solvents: a solvent that contains an –OH group, they are good for dissolving anions and cations. This increases the rate of S_N1 but decreases S_N2 by solvating the Nu. (water, alcohols, acids)
- Polar aprotic solvents: only solvate cations well therefore good for S_N2 as the Nu is very reactive in these conditions. (acetone, DMSO, DMF, acetonitrile)

Polar solvents ← بحبوا الـ SN1 و SN2 ← يستعمل لتسريع التفاعل

Protic ← عندما يكون Nu ضعيف

OH

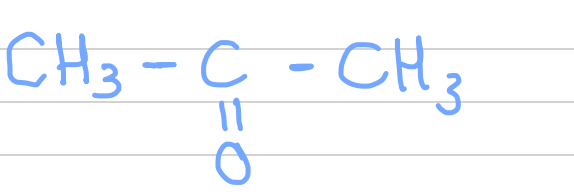
أمثلة

R-OH

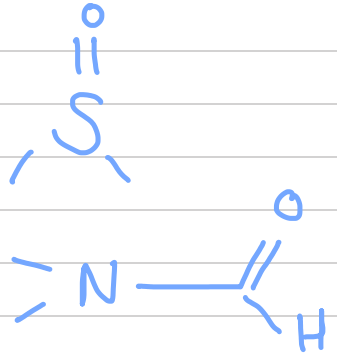
A-protic ← عندما تكون Base stronge

NO(OH)

أمثلة



CH_3CN



DMSO/DMF

بحبوا SN1

بحبوا SN2

شو يعني بحبوا ؟ يعني لما أضيفه لراد التفاعل بصير أسرع وهي

مش قاعدة ثابتة في إستثناءات

Nu ضعيف في Polar Protic SN1

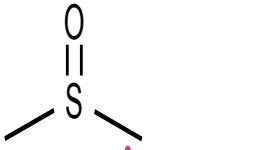
Strong base → polar aprotic.

S_N1 vs. S_N2: Solvent Effects

Effects of polar protic/aprotic solvent polarity on S_N2 mechanism

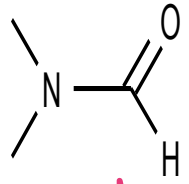
الأرقام موضحة

	Protic /aprotic Solvent		Relative Rate
Protic	CH_3OH		1
	H_2O		7
Aprotic	$(CH_3)_2SO$	(DMSO)	1,300
	$(CH_3)_2NCHO$	(DMF)	2,800
	$CH_3C{\equiv}N$		5,000



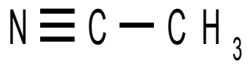
Aprotic

dimethyl sulfoxide



Aprotic

dimethylformamide



Aprotic

acetonitrile

Record 14
5:17

S_N1 vs. S_N2: Summary

ملخص سريع
للي تعلمناه

Summary of S_N1 & S_N2 reactions:

Variable	S_N1	S_N2
Halide: 1° primary	NO	YES
2° Secondary	Yes	Yes
3° tertiary	YES	NO
Stereochemistry	Racemization	Inversion
nucleophile	Neutral ok as rate doesn't depend on [Nu]	Best when anionic *
Solvent	Polar protic	Polar aprotic best, Polar protic slow

S_N1 vs. S_N2: Nucleophile

کلاه شرحناه

1) Anions are stronger nucleophiles than neutral molecules, i.e. HO^- vs. H_2O (but more basic).
2) Nucleophilic strength increases down a column in the Periodic Table (polarizability).
3) Across a row in the periodic table nucleophilicity (lone pair donation) $C^- > N^- > O^- > F^-$ since increasing electronegativity decreases the lone pair availability.

S_N1 vs. S_N2: Summary

کاه شرحناه

Summary of S_N1 & S_N2 reactions:

- 1 ° - react S_N2! Can't make stable carbocation
- 3 ° - react S_N1! Too sterically crowded for S_N2
- 2 ° - reacts either S_N1 or S_N2, this is the one you have to use nucleophilic strength and solvent conditions to control the mechanism if needed.

Record 14
7:00

$\ddot{O}H^- + CH_3X \longrightarrow CH_3OH$

- هاد التفاعل عبارة عن Nucleophilic substitution

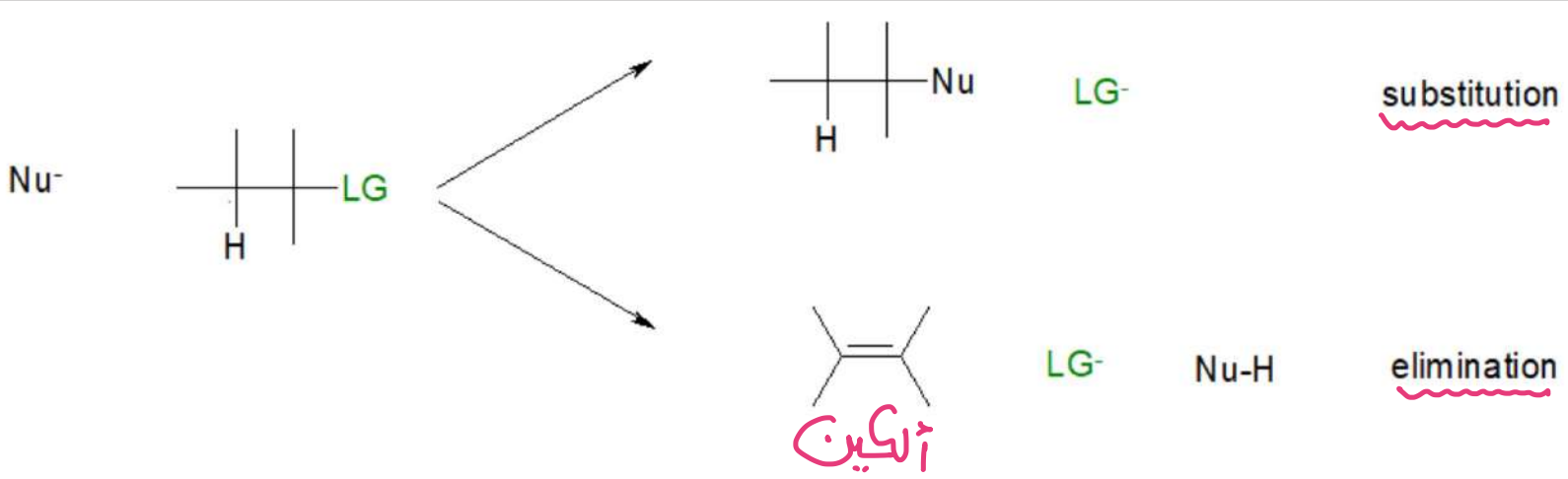
- ال OH هجمت من backside وطلعت X LG 's وحطينا مكانها Product.

ملاحظة: ال OH^- بنقدر نشوفها بالتفاعلات 's:

Nucleophile
Strong base ← NaOH / KOH

- لما تكون OH متصرفة Strong base 's بدها تحصل على ألكين.

بهاي الحالة بسمي التفاعل ← Elimination



Record 14
10:30

OH^- + CH_3X ⟶ CH_3OH

OH^- = Nu anion

Neutral

+ R-X ⟶ R-Ö(H)H

very acidic
وسهل يفقد H^+

حيكمل التفاعل ⟶ ROH ⟶ lone pair ↓ (+) on oxygen

الملخص:-

1. عند استخدام Anion ← يعمل مباشرة على ← Neutral

2. اذا استخدمت Neutral ← مرتب Charged (+) ← يفقد H^+ ← Neutral

↳ حتلاقوا أمثلة كتيرة بالمحدرك

Table 6.1 Reactions of Common Nucleophiles with Alkyl Halides (Eqs. 6.2 and 6.3)

Nu		R—Nu		
Formula	**Name**	**Formula**	**Name**	**Comments**
Oxygen nucleophiles				
1. HO^-	hydroxide	R—OH	alcohol	These ions lose a proton and the products are alcohols and ethers.
2. RO^-	alkoxide	R—OR	ether	
3. HOH	water	$R-\overset{+}{O}(H)H$	alkyloxonium ion	
4. ROH	alcohol	$R-\overset{+}{O}(R)H$	dialkyloxonium ion	
5. $R-C(=O)-O^-$	carboxylate	$R-OC(=O)-R$	ester	
Nitrogen nucleophiles				
6. NH_3	ammonia	$R-\overset{+}{N}H_3$	alkylammonium ion	With a base, these ions readily lose a proton to give amines.
7. RNH_2	primary amine	$R-\overset{+}{N}H_2R$	dialkylammonium ion	
8. R_2NH	secondary amine	$R-\overset{+}{N}HR_2$	trialkylammonium ion	
9. R_3N	tertiary amine	$R-\overset{+}{N}R_3$	tetraalkylammonium ion	
Sulfur nucleophiles				
10. HS^-	hydrosulfide	R—SH	thiol	
11. RS^-	mercaptide	R—SR	thioether (sulfide)	
12. R_2S	thioether	$R-\overset{+}{S}R_2$	trialkylsulfonium ion	
Halogen nucleophiles				
13. I^-	iodide	R—I	alkyl iodide	The usual solvent is acetone. Sodium iodide is soluble in acetone, but sodium bromide and sodium chloride are not.
Carbon nucleophiles				
14. $^-:C\equiv N:$	cyanide	$R-C\equiv N:$	alkyl cyanide (nitrile)	Sometimes the isonitrile, $R-N\equiv C:$, is formed.
15. $^-:C\equiv CR$	acetylide	$R-C\equiv CR$	alkyne	

الفكرة من الجدول هي :

- Nucleophile موشرط يكون عليط (-) .
- ال electron density حولط عالي .
- فلو كان عليط lone pairs حتشتغل بالشكل الطبيعي بحيث ال Product الأول حيكون protonated

فلو عندها H حتفقد هاي ال H وبعدها حنحصل على Neutral product .

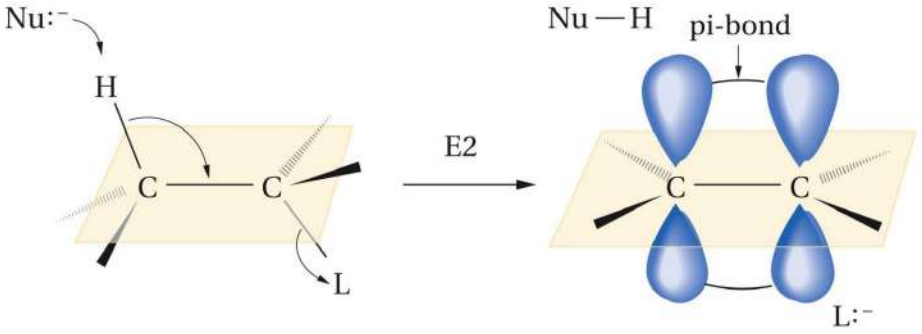
Record 14
18:00

ركزوا منيح

نرجع على فصة الـ Stronge base :

- الـ Stronge base الطلوبين منا هم : HO^- و RO^- stronge base + very good Nu →
ولكن I^- عكسهم هي Good electrophile ولكنها weak base .

- عملية الـ Elimination الها 2 Types : ① E2 ② E1



① E2 mechanism :

- بصير عنا Elimination للهيدروجينة الي بتكون anti مع LG الي هي X حسب ما هو مطلوب منا .
- الي بصير كالتالي ←

بيجي الـ Nu والي هو stronge base بيسحب الـ H و بترك وراه e^- على المنطقة بين C - C والي حتعمل فيهم double bond ، و الـ LG حتطلع ، فبالنهاية حنحصل على ألكين بـ 1 Step .

طيب شو الفرق بينها وبين SN2

SN2 ← Nu بهاجم من back side لـ C - X وممنوع يمشي مع الـ Tertiary .

E2 ← هجوم عالـ H المرتبطة مع C الي بتكون anti مع LG وممكن تمشي مع الـ 3° 2° 1° لأنو عالي صعوبة لفصل الـ C

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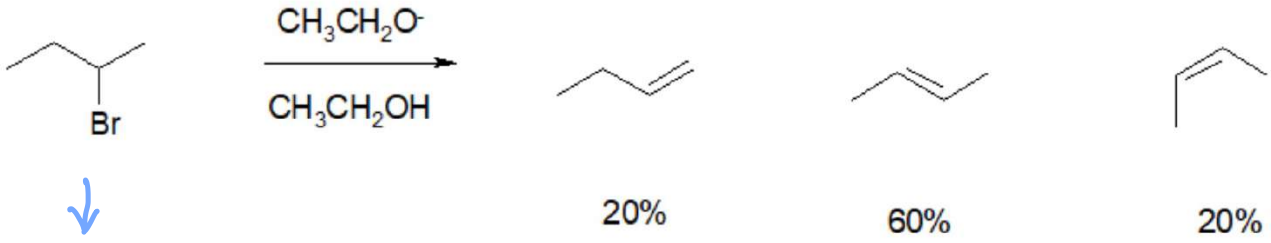
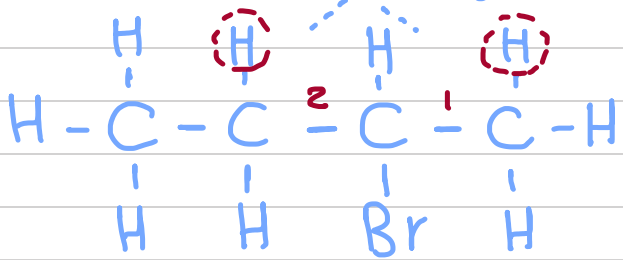
25:00

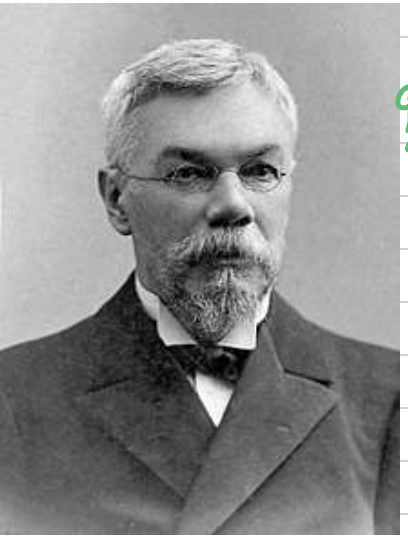


2° halide alkyle



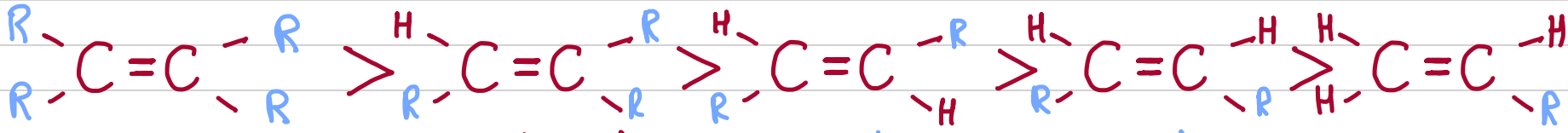
* لو بدي أكون double bond فأنا بقدر أكونها بـ 1 أو 2 ، طيب مين نختار ؟

هذا ما جاوبنا عليه عمو زت سيف بـ (Zaitsev rule) (اسمه متعوب عليه)

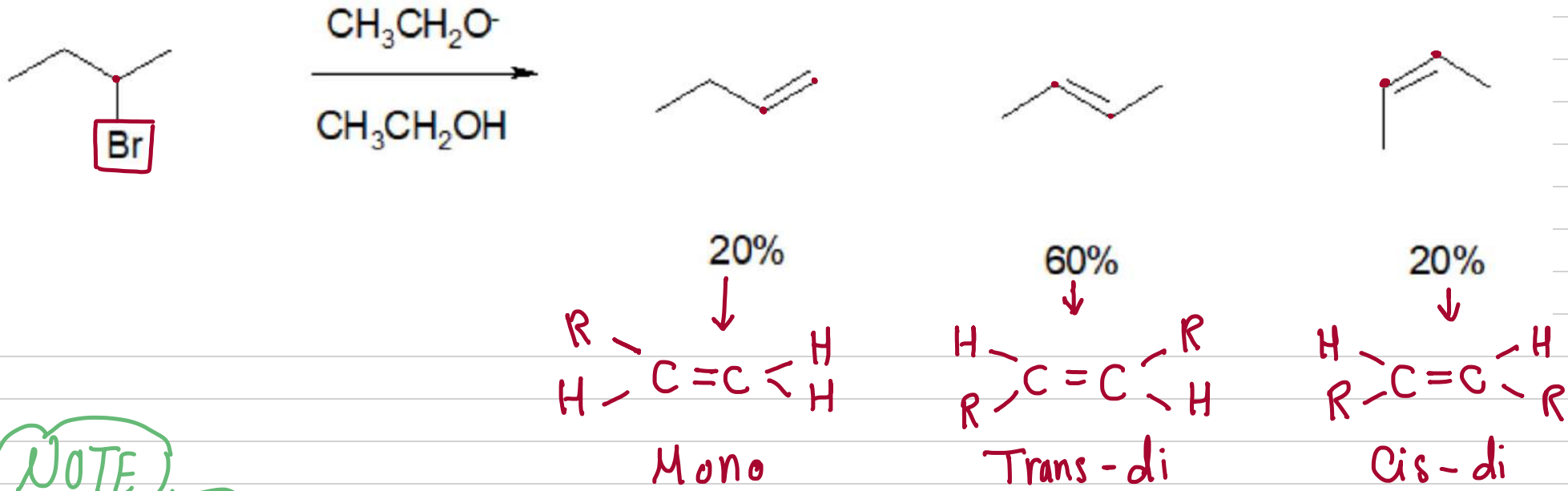


* عمو زيت سيف حكالنا إنه حنختار C=C اللي حولها R أكثر ، ليش؟ لأنها بتكون أكثر إستقرارًا .

* مهم جدًا *



نرجع المثال مثلاً:



NOTE

الدكتورهون نبعنا عكن يجي سؤال معادلة ويسألك زي Major خيار هو ال بالحالة لازم تدور على الأعلى استقراراً

Major ← فبنحكي عنه ← is more stable

② E1 mechanism :. * Several Steps *

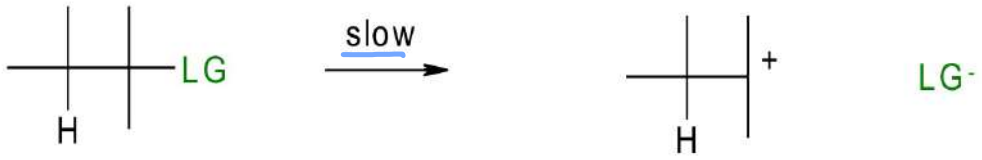
① الخطوة الأولى بنشط تبعت SN1 ← Ionization وتكوين Carbocation ← Slow .

② خطوة رقم 2 الها احتمالين : الأول ← SN1 : Nu مع Carbocation

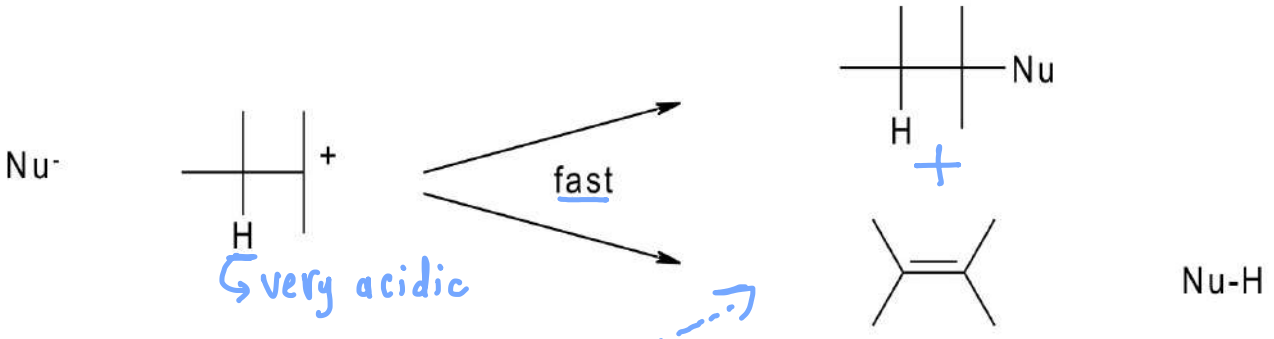
الثاني ← : Nu بيعمل abstract لـ H واللي بتكون very very acidic

* والاثنين بكونوا Fast *

Step 1 :



Step 2:



عادة بالتفاعلات SN1 برافقه E1 وهدول 2products بكونوا مع بعض .

Elimination Reactions

A problem arises in nucleophilic substitution reactions in that nucleophiles are also bases. This is especially true for anionic nucleophiles, i.e.

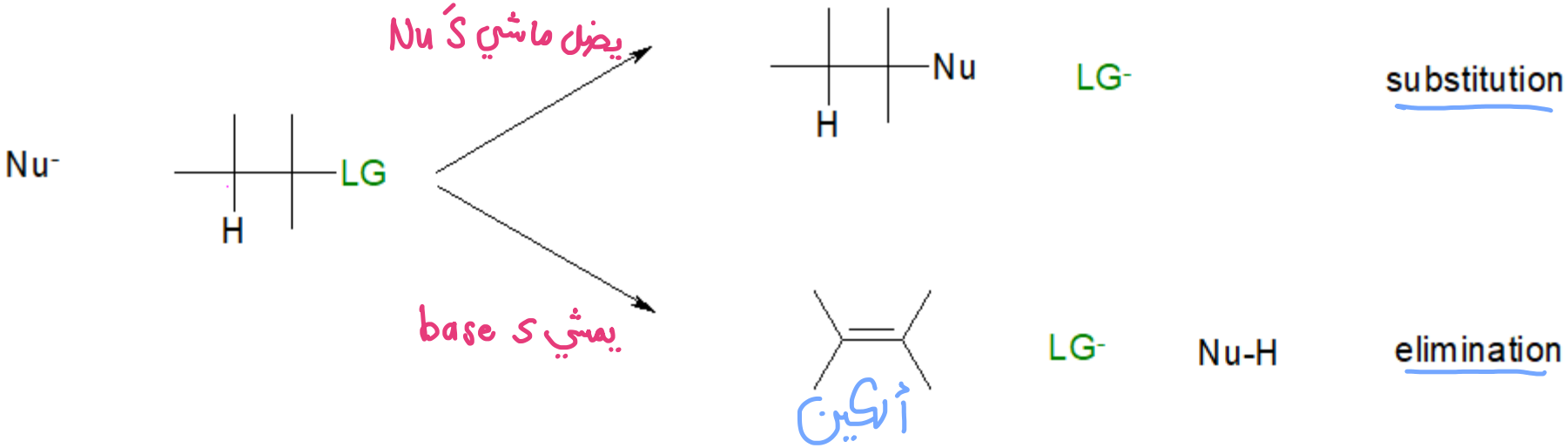
$$Nu:^- + H^+ \rightarrow Nu:H \text{ (Nu-H)}$$

This can occur by the Nu abstracting a proton (i.e. acting as a base) from the substrate giving an elimination reaction.

Dehydrohalogenation Reactions

A dehydrohalogenation is an elimination reaction of alkyl halides. It will compete with a substitution to some degree, i.e.

مقارنة بين التفاعلين



It is used to produce alkenes from alkyl halides

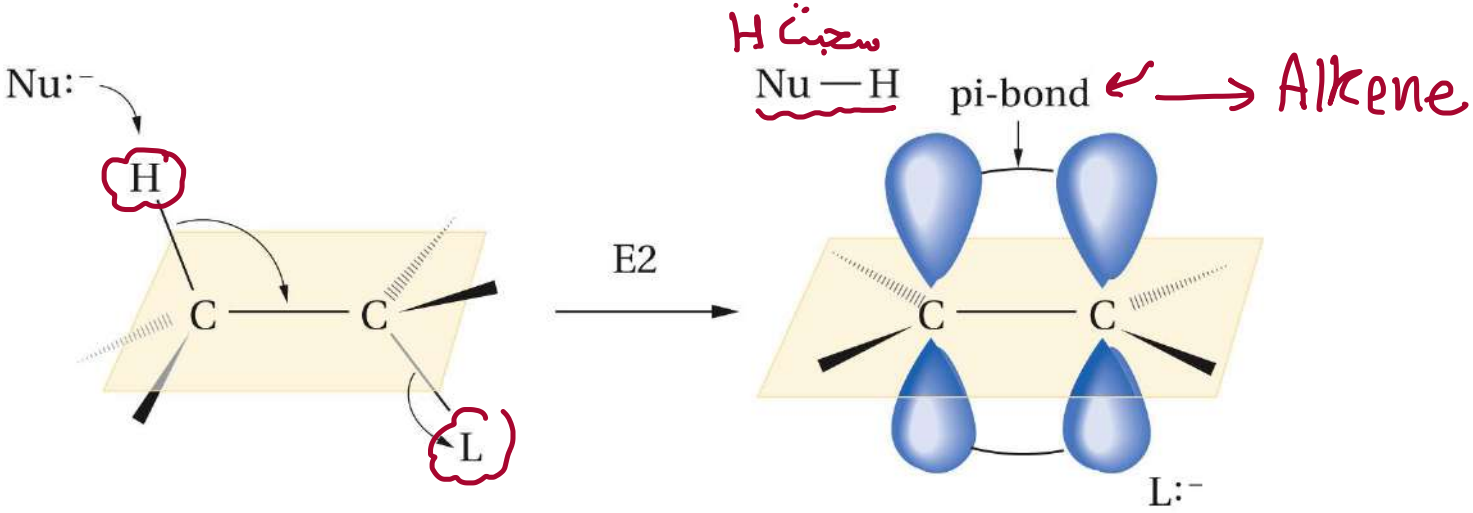
E Mechanisms

SN2
SN1

Like substitution there are several possible mechanisms for elimination reactions. We will examine two of them: E1 and E2

E2 Mechanism

- Rate = k[alkyl halide][base] (bimolecular)
- Stereochemical requirement: anti-periplanar arrangement of the H atom and LG is required
  - This results from an orbital interaction that allows the π bond to form.

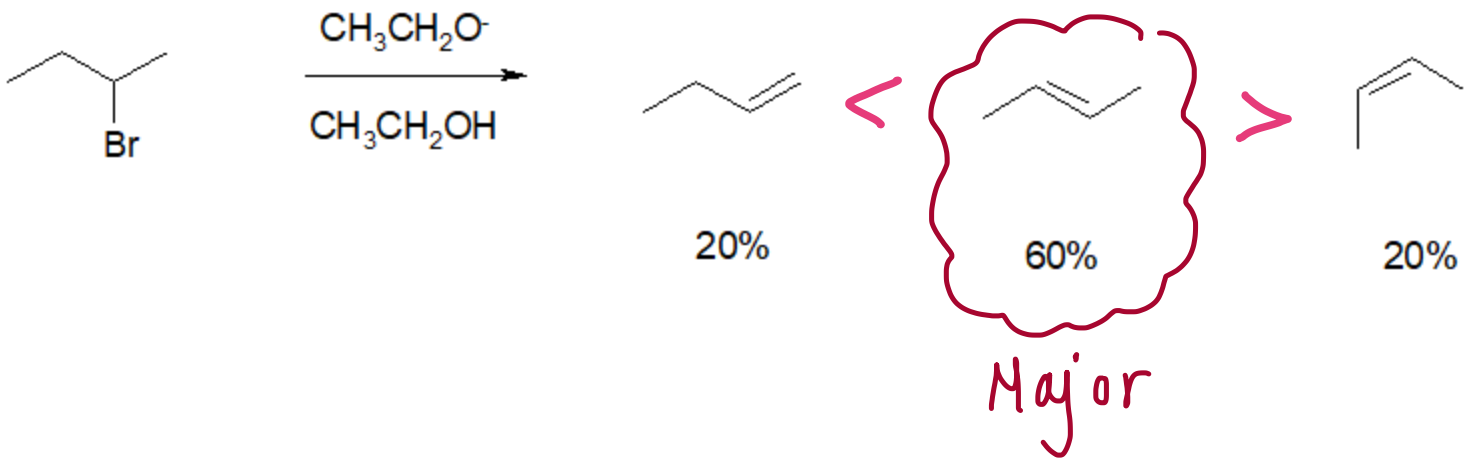


E2 Mechanism

کلیک‌شرحناه

Regioselectivity: where does the double bond form: *Zaitsev's rule*: most highly substituted alkene (watch for sterically hindered bases)

Stereoisomers: trans > cis



E1 Mechanism

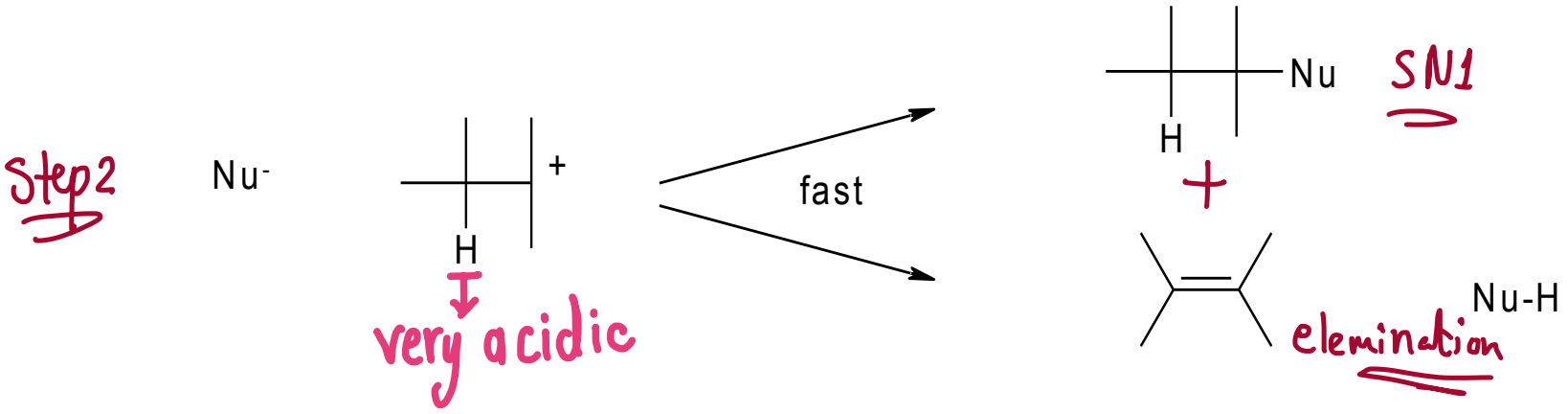
E1 زائد SN1

SN1 زي

- Rate = k[alkyl halide] (unimolecular)

Step1

Step2



Summary of S_N versus E for Haloalkanes

(هاد الجدول مقسم حسب نوع Alkyle Halide)

هاد الجدول مهم حيساعدنا على حل الأسئلة

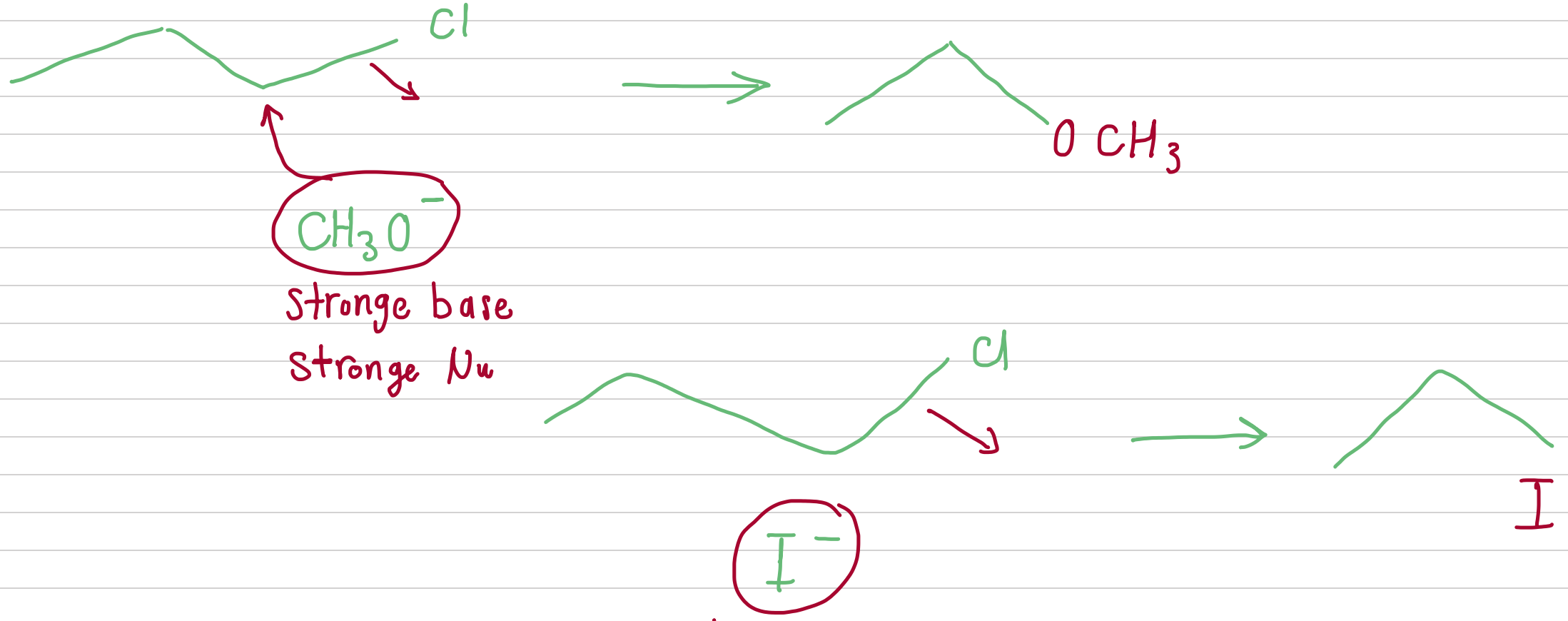
① – For Methyl and Primary Haloalkanes

↳ SN1 مستحيل

TABLE 7.7 Summary of Substitution versus Elimination Reactions of Haloalkanes

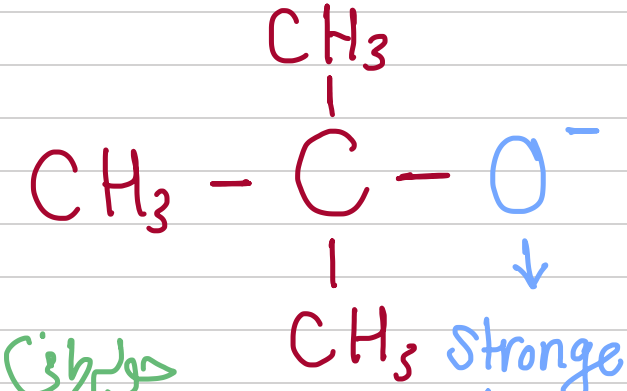
Halide	Reaction	Comments
Methyl CH_3X	S_N2	The only substitution reactions observed.
	~~S_N1~~	S_N1 reactions of methyl halides are never observed. The methyl cation is so unstable that it is never formed in solution.
Primary RCH_2X	S_N2	The main reaction with strong bases such as OH^- and EtO^-. Also, the main reaction with good nucleophiles/weak bases, such as I^- and CH_3COO^-. RS^-, HS^- → SN2 بيمشو
	E2	The main reaction with strong, bulky bases, such as potassium *tert*-butoxide.
	~~S_N1/E1~~	Primary cations are never formed in solution; therefore, S_N1 and E1 reactions of primary halides are never observed.

* SN2 mech. in primary :-



* سجل على SN2 انه يمشي بال Primary ، السبب هو لانه بيحاجم من backside غاني كيث R بنكل سهولة بيجي عقروب X وبطلعه LG .

الدكتور حكى لوجبتلك سؤال :-



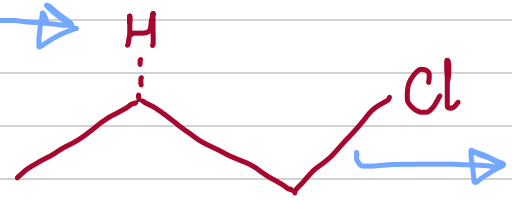
حولوطي كتير R

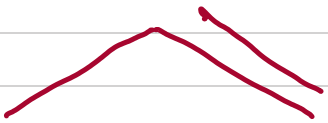
Stronge base

↳ back side شوي صعب يوصل لـ N

↓

فبيعمل Elimination بياخد H





Elimination 2

الملخص

- لو كان حجم Stronge base حبتين زي RO^- , OH^- و weak base, good Nu

حيمشي SN_2 مع الـ Primary .

- لو كان عنا الحجم كبير و Bulky صعب Nu يوصل لـ N back side فبروح يعمل E2 .

Summary of S_N versus E for Haloalkanes

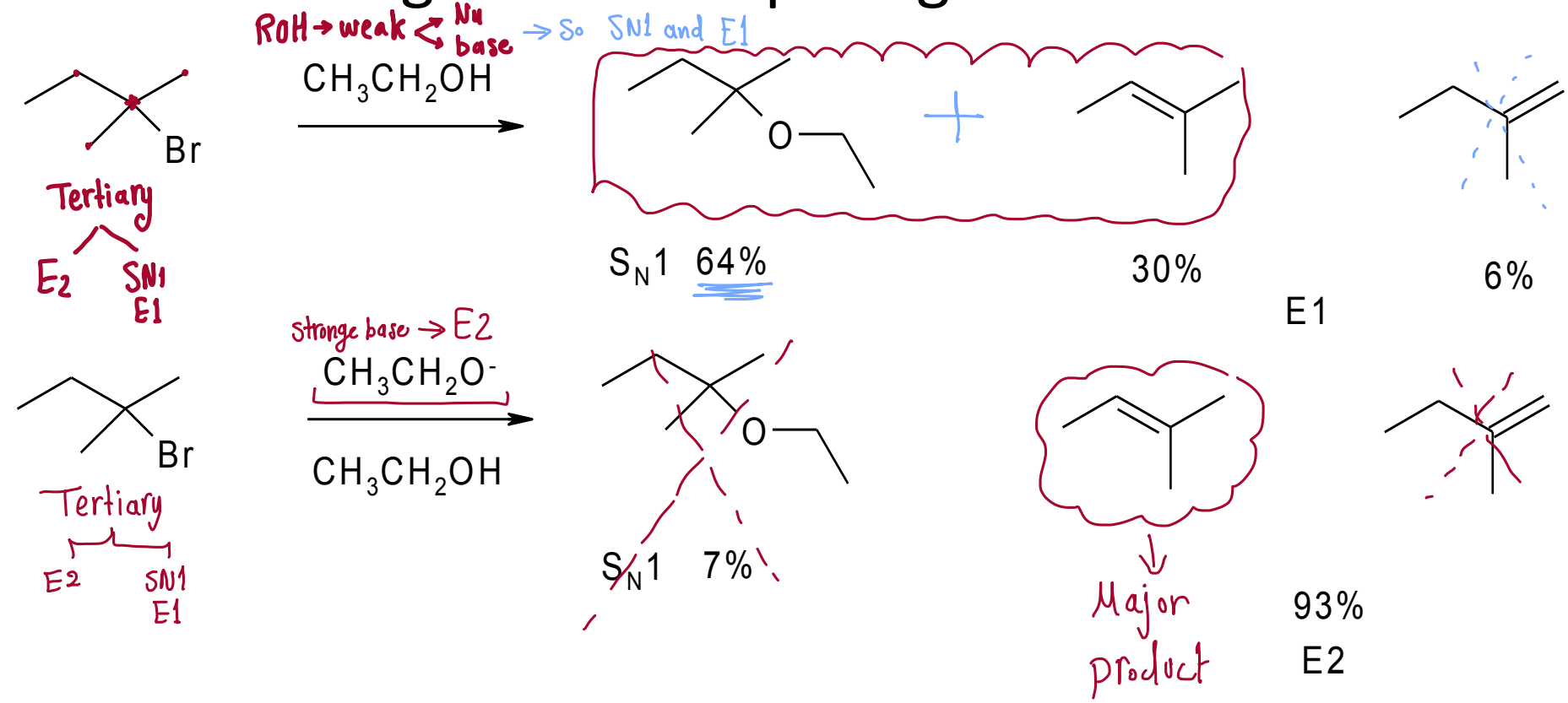
– For Secondary and Tertiary Haloalkanes

TABLE 7.7 Summary of Substitution versus Elimination Reactions of Haloalkanes

Halide	Reaction	Comments
Secondary R_2CHX	S_N2	The main reaction with weak bases/good nucleophiles such as I^- and CH_3COO^-.
	E2	The main reaction with strong bases/good nucleophiles, such as OH^- and $CH_3CH_2O^-$.
	$S_N1/E1$	Common in reactions with weak nucleophiles in polar protic solvents, such as water, methanol, and ethanol.
Tertiary R_3CX	~~S_N2~~	S_N2 reactions of tertiary halides are never observed because of the extreme crowding around the 3° carbon.
	E2	Main reaction with strong bases such as HO^- and RO^-.
	$S_N1/E1$	Main reactions with poor nucleophiles/weak bases.

E1 Mechanism

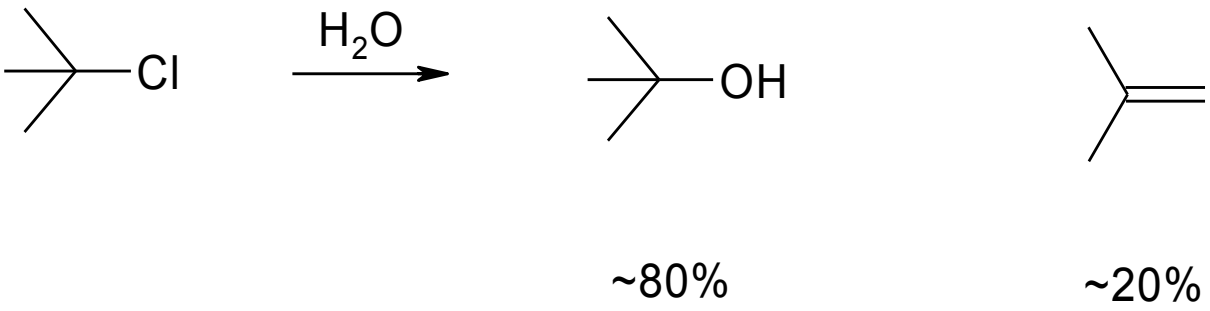
Base strength and competing mechanisms:

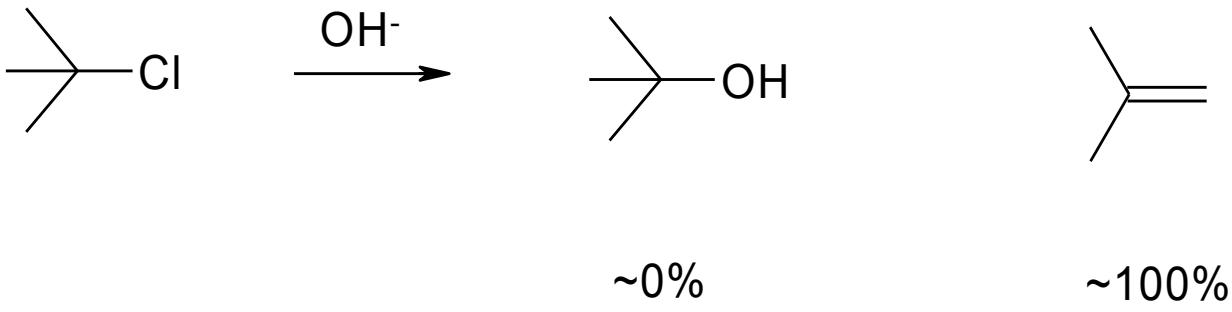


Substitution vs. Elimination

3° alkyl halides: only S_N1 but either (E1 or E2)

– Weak Nu and polar solvent: S_N1 and E1 compete





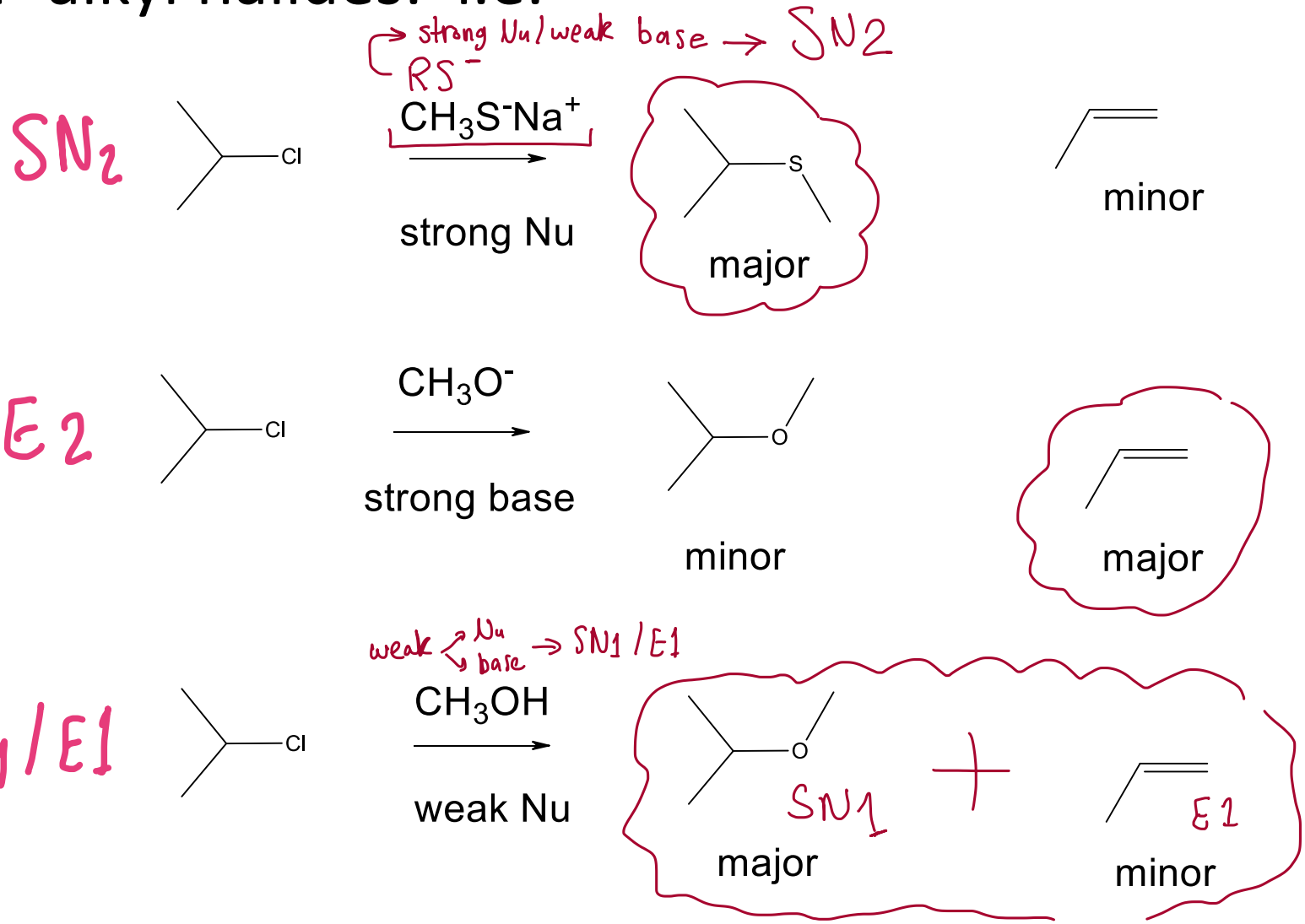
Substitution vs. Elimination

2° alkyl halides: S_N1, S_N2, E1 or E2 are all possible.

- Weak Nu → substitution
- Strong base → elimination
- Can use solvent to control S_N1 vs. S_N2

Substitution vs. Elimination

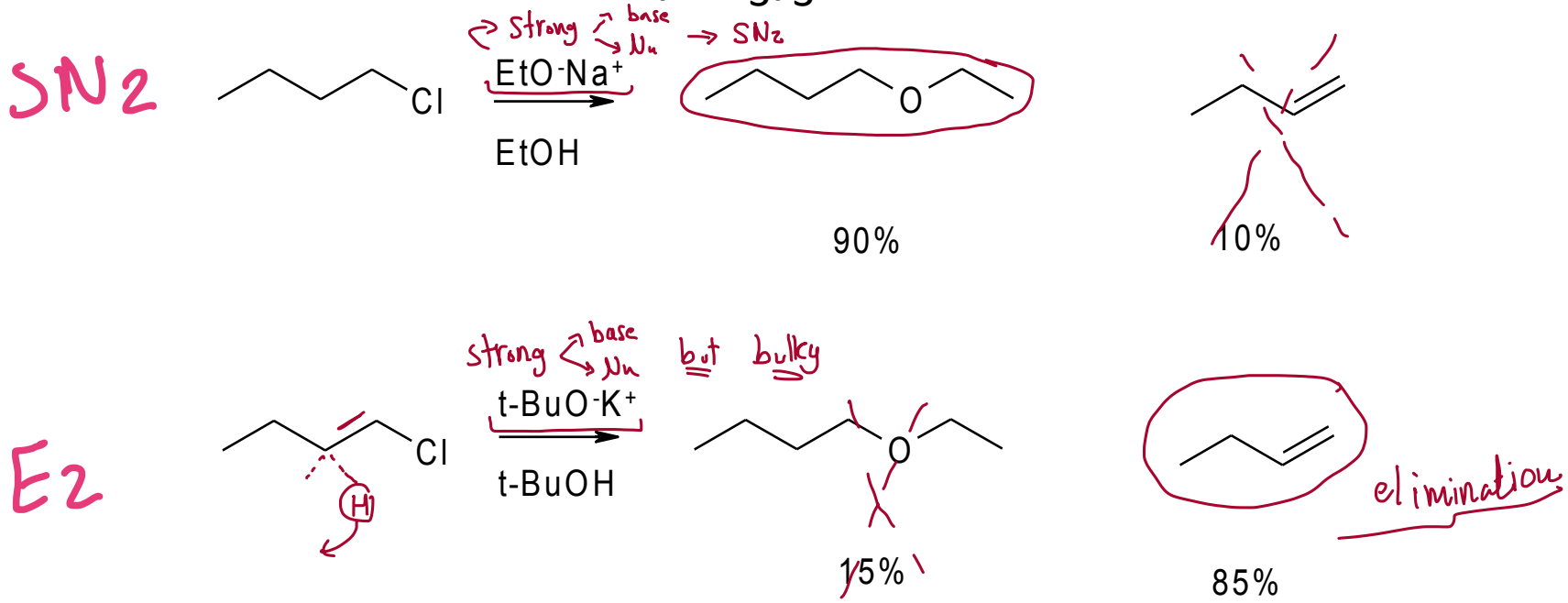
2° alkyl halides: i.e.



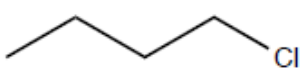
Substitution vs. Elimination

1° alkyl halides:

- Only S_N2 and E2 are possible (no carbocations)
- Substitution dominates unless you use a sterically hindered base like $(CH_3)_3CO^-K^+$

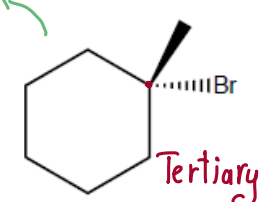


جربوا حلوهم ، الجمعة حننشر الحل ت



KCN
DMSO

50:45 اكل ريكورد ١٤



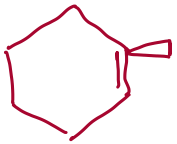
Tertiary

weak base / Nu
H_2O

SN1 + E1 →

SN1

+

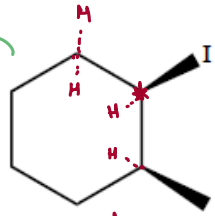


E1

2products

اكل ريكورد ١٤
48:00

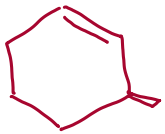
**



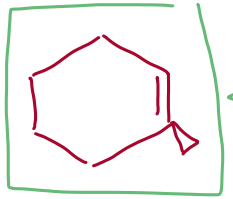
Secondary

Strong base / Nu
$CH_3CH_2O^-Na^+$
ethanol

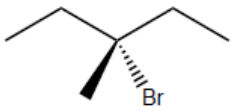
E2 →



أو



ولكن هاد هو Major ← حسب قانون هناك العمو



CH_3OH / H_2O

الحل ريكورد ١٩
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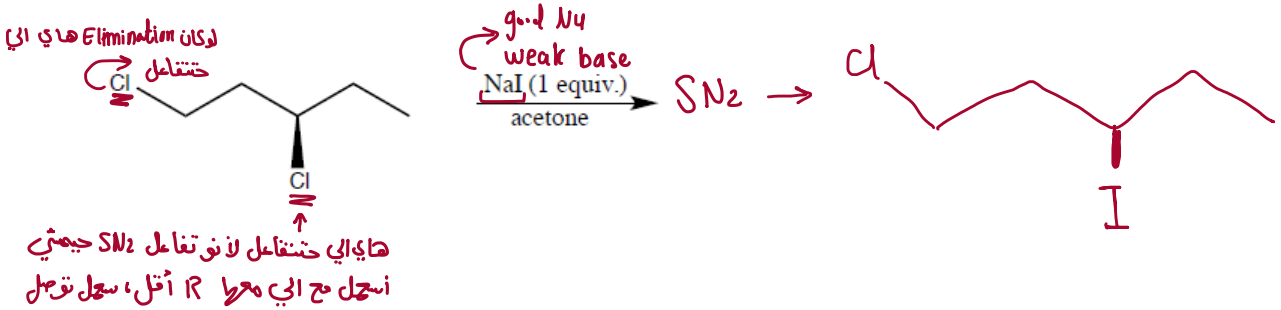

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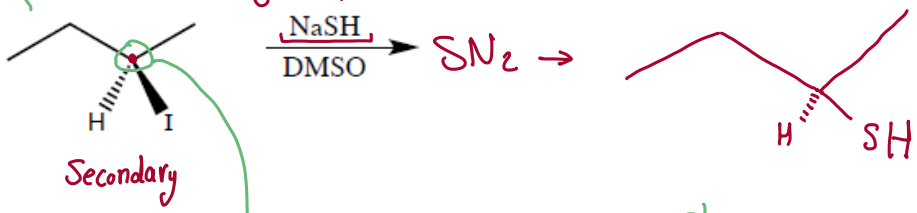
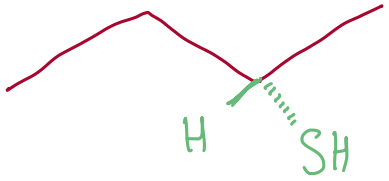
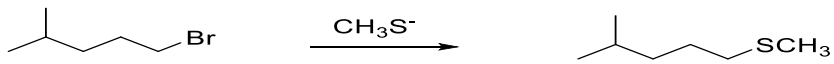


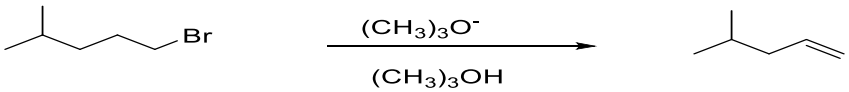
Secondary

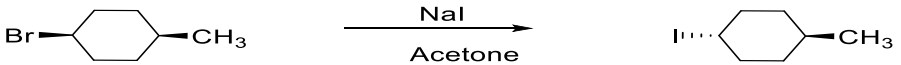
Chiral الذي ايزظ

Stereochem S
يعتبر غلط
الصح

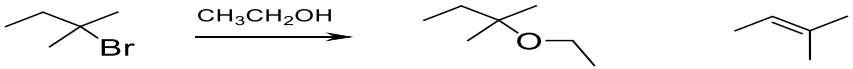



Br
CH_3S^-
SCH_3


Br
$(CH_3)_3O^-$
$(CH_3)_3OH$

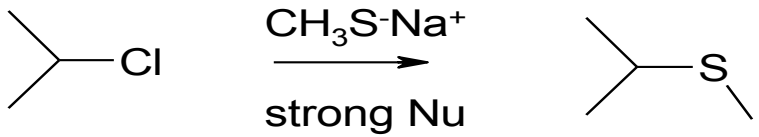

Br
CH_3
NaI
Acetone
I
CH_3

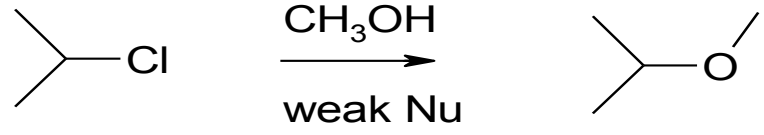

Br
CH_3OH
OCH_3
+
OCH_3
+


Br
CH_3CH_2OH
O

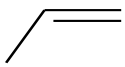

Br
$CH_3CH_2O^-$
CH_3CH_2OH

93%
E2





major



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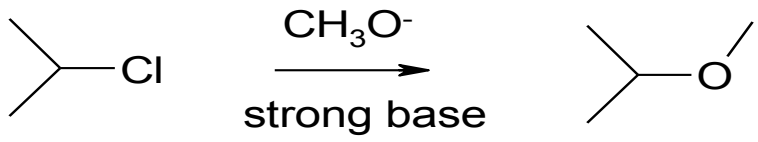
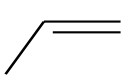


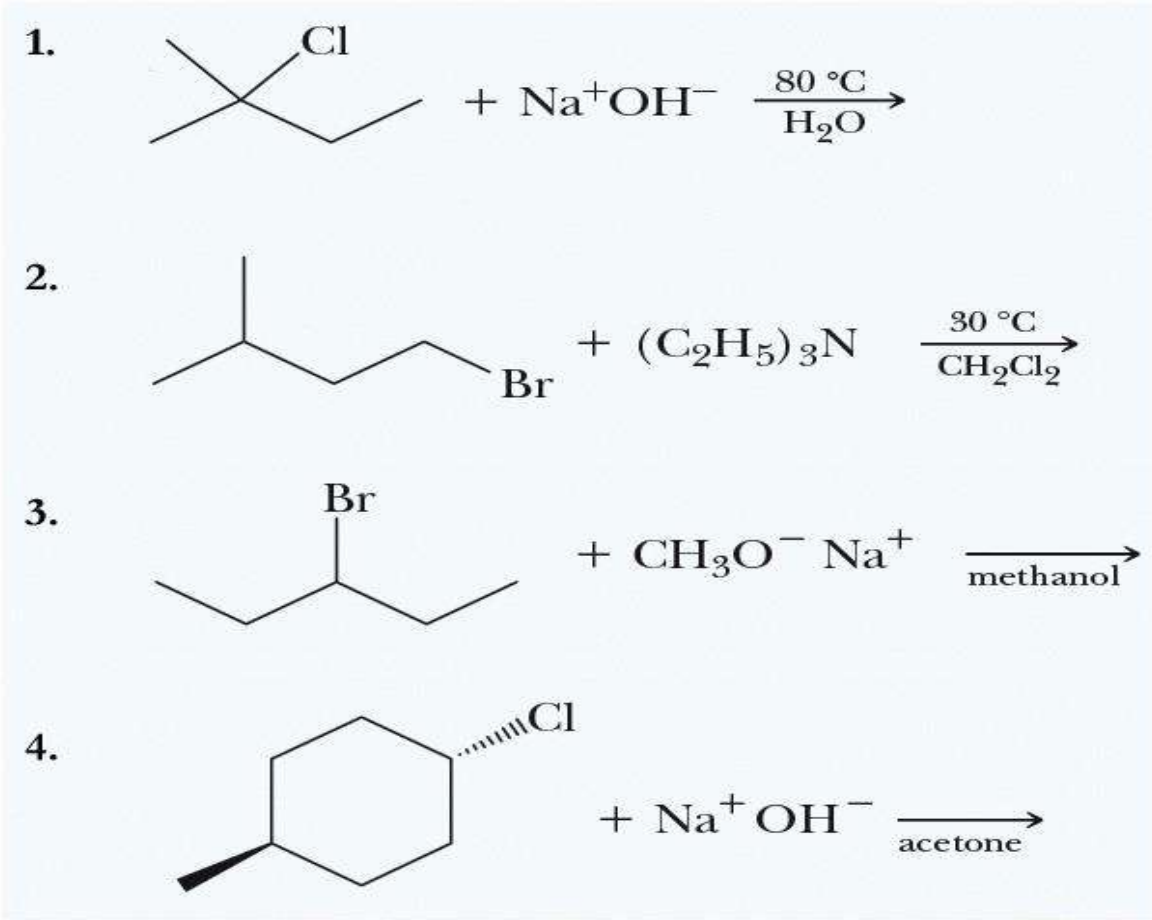
minor



major

Summary of S_N versus E for Haloalkanes

- **Examples**: Predict the **major** product and the **mechanism** for each reaction.



هناك أناس يتفننون في جعل الممكن مستحيلا ، بينما آخرون :
يبتكرون ليجعلوا من المستحيل ممكنا .
لا تكترثوا بالصنف الأول و كونوا كالصنف الثاني

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