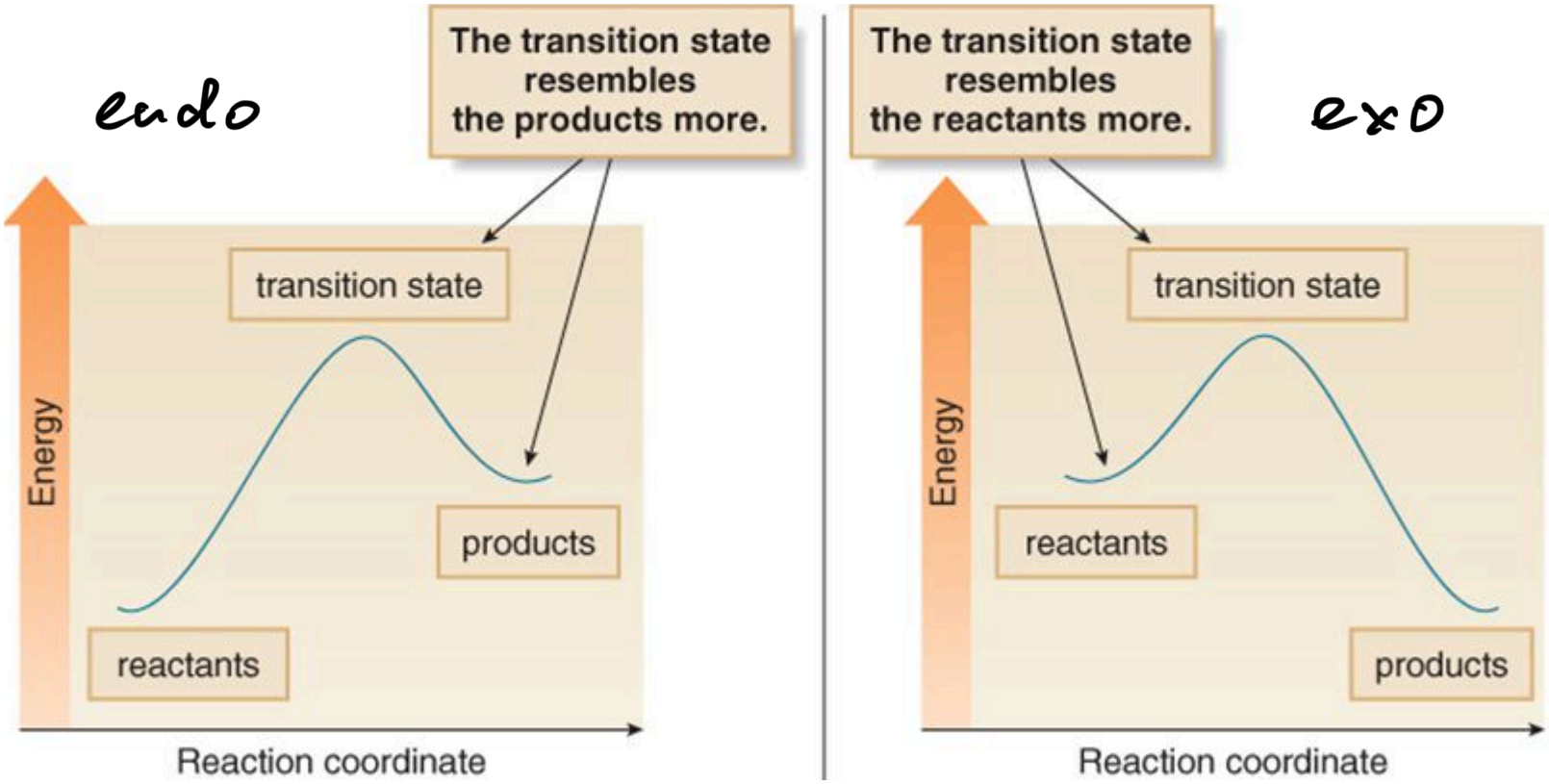
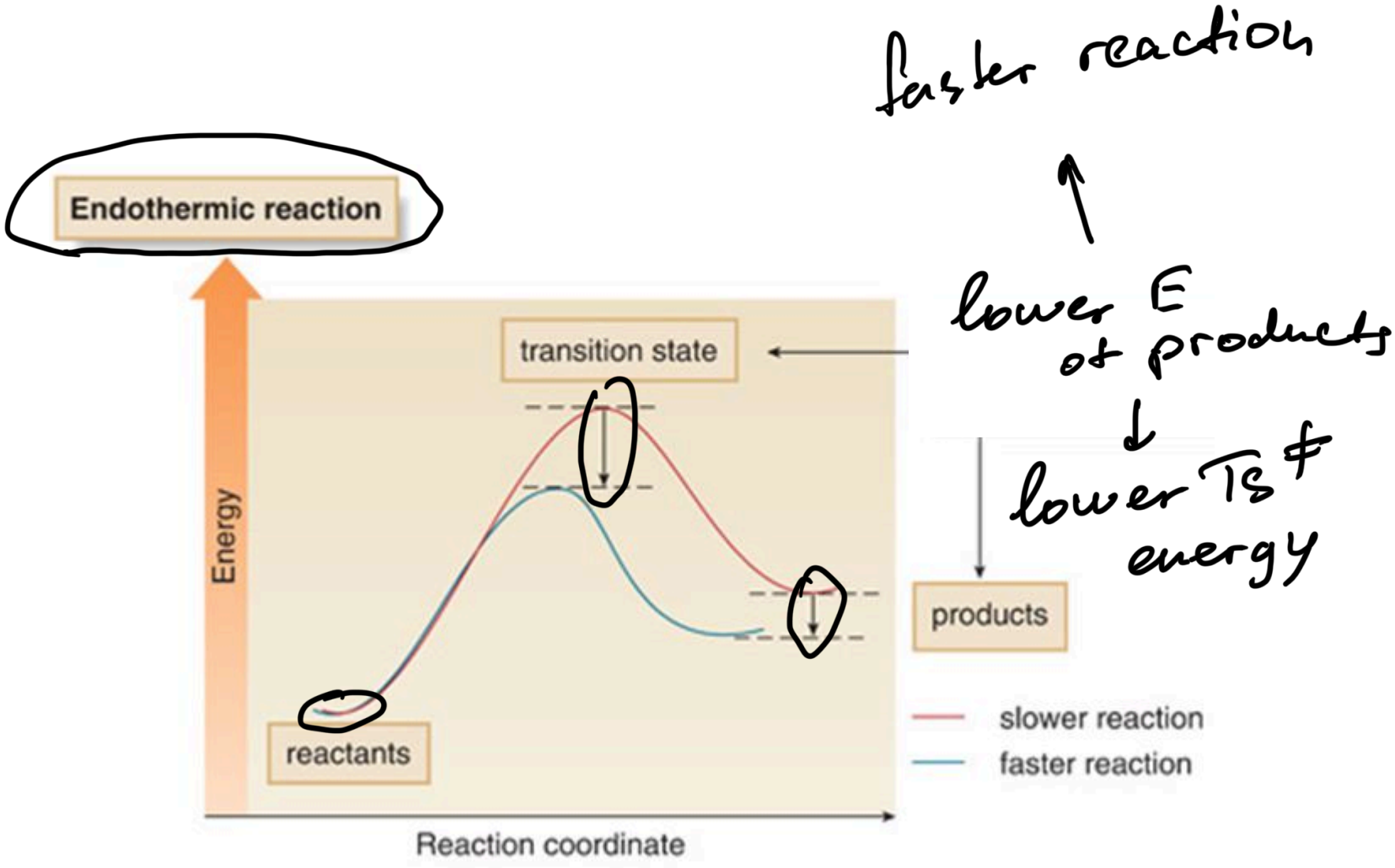
Nucleophilic substitution: the S_N1 mechanism

The Hammond postulate : relate TS‡ energy and relative energies of SM and P



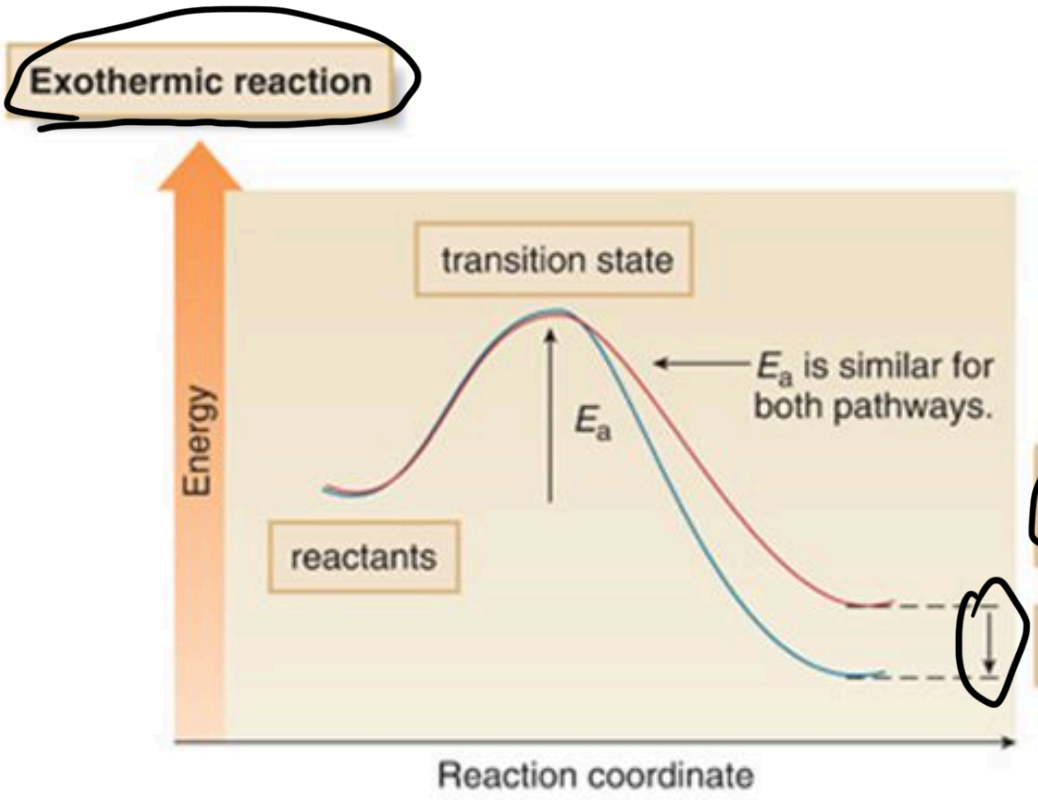
Nucleophilic substitution: the S_N1 mechanism

The Hammond postulate



Nucleophilic substitution: the S_N1 mechanism

The Hammond postulate

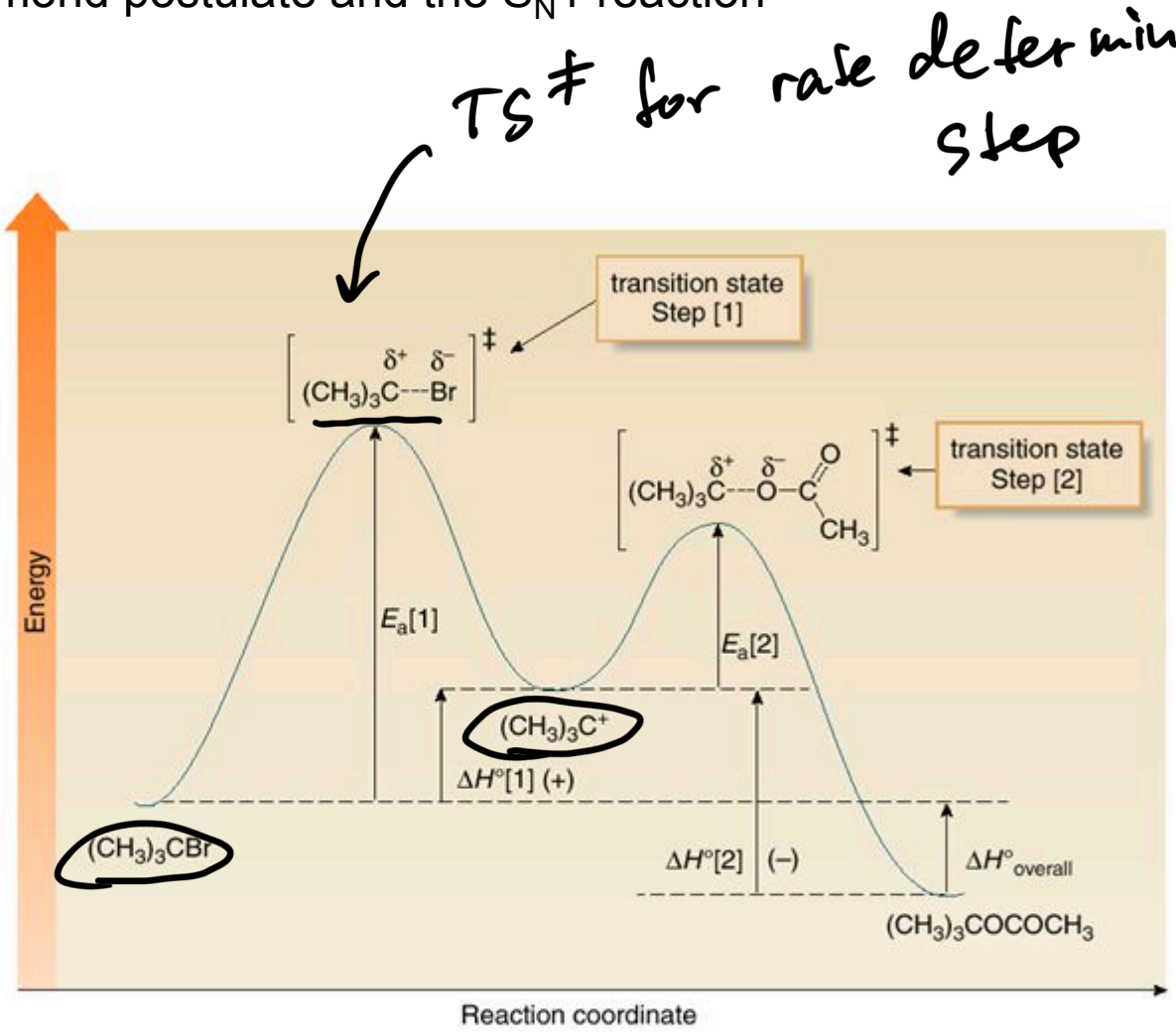


no change in the rate of the reaction

Decreasing the energy of the product has little effect on the energy of the transition state.

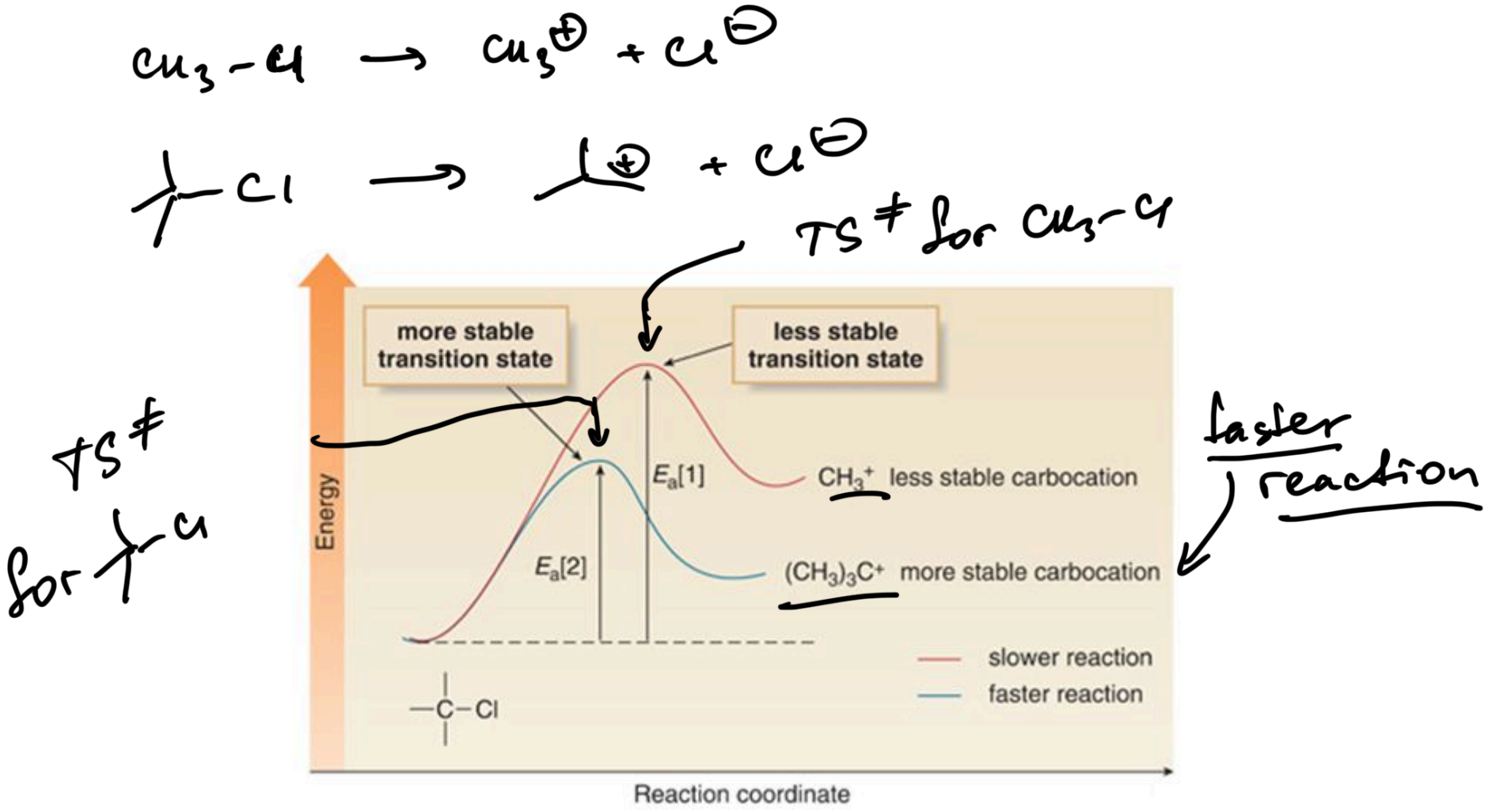
Nucleophilic substitution: the S_N1 mechanism

The Hammond postulate and the S_N1 reaction



Nucleophilic substitution: the S_N1 mechanism

The Hammond postulate and the S_N1 reaction



Nucleophilic substitution: S_N2 or S_N1 mechanism?

Factors governing the mechanism of the substitution reaction

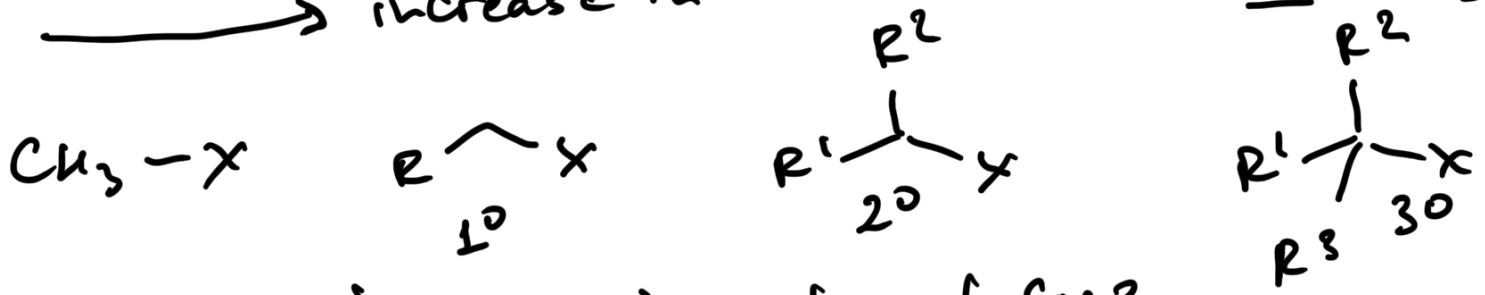
- structure of alkyl halide
  - the most important
  - structure of R group
- nucleophile
- leaving group
- solvent

Nucleophilic substitution: S_N2 or S_N1 mechanism?

Effect of the alkyl group

- CH_3 - & 1^0 by S_N2 only
- !!! → 2^0 either S_N2 or S_N1
- 3^0 → by S_N1 only

→ increase in rate of S_N1



← increase in rate of S_N2

for S_N2: steric factor ← opposite trends

for S_N1: stability of the resulting carbocation

Nucleophilic substitution: S_N2 or S_N1 mechanism?

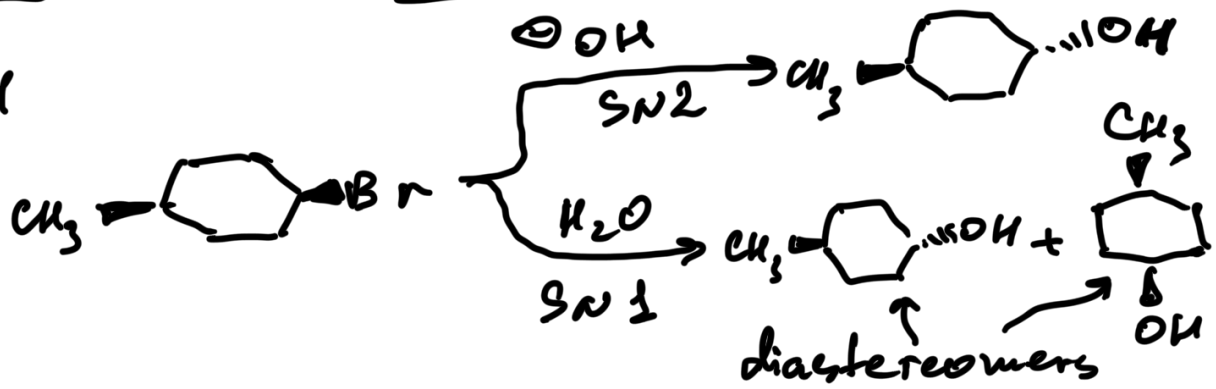
Effect of the nucleophile

for S_N2 : rate $= k[R\text{-}X][Nu^{\ominus}]$

for S_N1 : rate $= k[R\text{-}X]$

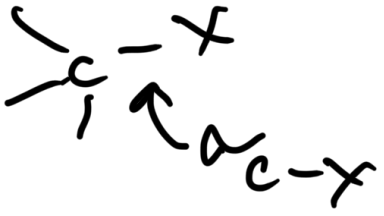
- charged Nu, high concentration of Nu
  $^{\ominus}OH$, $^{\ominus}CN$, $^{\ominus}N_3$, $PhS^{\ominus}$ will favor S_N2
- neutral, weak Nu will favor S_N1

  H_2O, R-OH



Nucleophilic substitution: S_N2 or S_N1 mechanism?

Effect of the leaving group

- better leaving group
  ↓
  faster S_N2 and S_N1
  ↓
  easier to break  σ_{C-X}

R-F R-Cl R-Br R-I

increasing leaving group ability

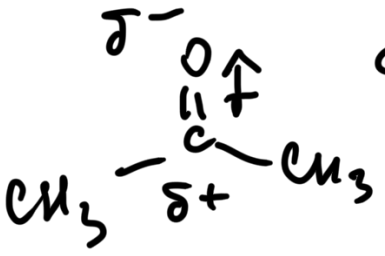
Nucleophilic substitution: S_N2 or S_N1 mechanism?

Effect of the solvent : polar protic and polar aprotic

- polar protic solvents favor S_N1 reactions (good for)

H_2O, R-OH $\longrightarrow$ $-\overset{\delta-}{O}-H\,\delta+$ solvate both cations and anions (ion-dipole interactions)

- polar aprotic solvents $\longrightarrow$ good for S_N2



solvate cations

↓

"naked" anions

Nucleophilic substitution: S_N2 or S_N1 mechanism?

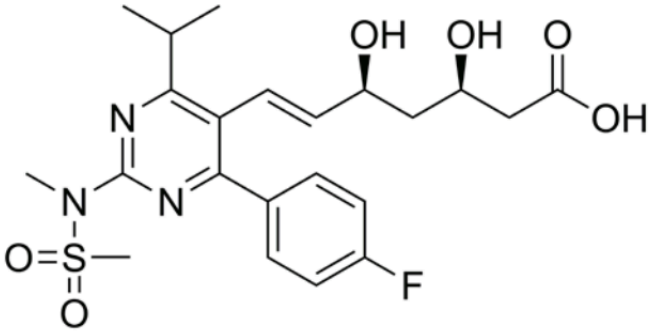
Case studies

Organic synthesis

Organic synthesis

20 **Crestor**

(Rosuvastatin)



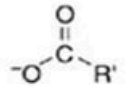
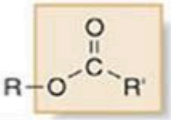
AstraZeneca

$3,401 Million

Cardiovascular Diseases

Organic synthesis

Organic synthesis and nucleophilic subsitution

	Nucleophile (:Nu⁻)	Product	Name
Oxygen compounds	^-OH	R—OH	alcohol
	$^-OR'$	R—OR'	ether
			ester
Carbon compounds	^-CN	R—CN	nitrile
	$:C\equiv C-H$	R—C≡C—H	alkyne
Nitrogen compounds	N_3^-	R—N_3	azide
	$:NH_3$	R—NH_2	amine
Sulfur compounds	^-SH	R—SH	thiol
	$^-SR'$	R—SR'	sulfide

Organic synthesis

Organic synthesis and nucleophilic subsitution

Organic synthesis

Organic synthesis and nucleophilic subsitution