TÁMOP-4.1.1.F-14/1/KONV-2015-0006
SZTE TTIK, KTCS, 1a) Duális és moduláris képzésfejlesztés a mesterképzéshez

# Nukleofil szubsztitúciós és eliminációs reakciók 1.

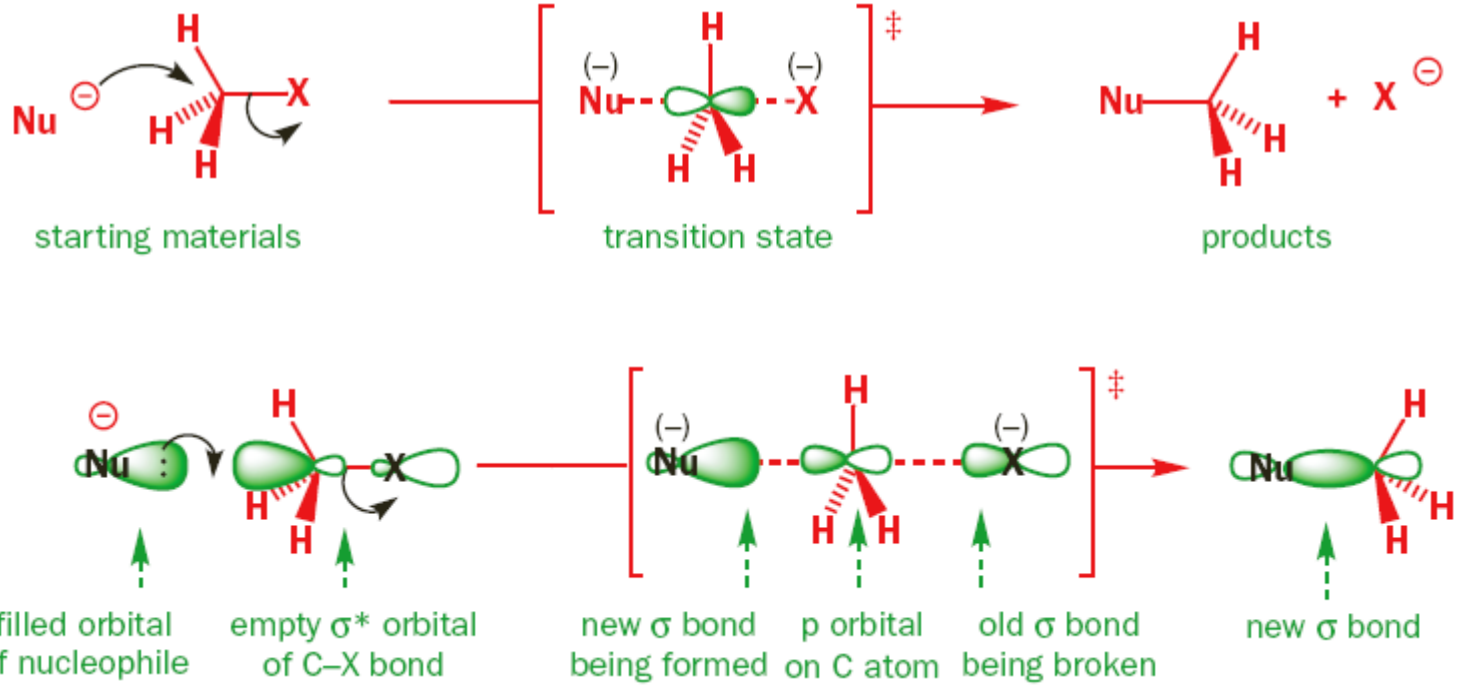
Pálinkó István, egyetemi tanár

SZÉCHENYI 2020
MAGYARORSZÁG KORMÁNYA
Európai Unió
Európai Szociális Alap
BEFEKTETÉS A JÖVŐBE

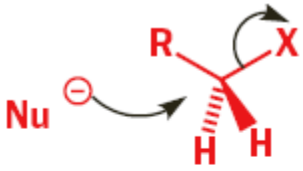
a kétféle reakció együtt jár – közöttük vagy direkt, vagy indirekt versengés van

# Általános kép

## $S_N2$ reakció

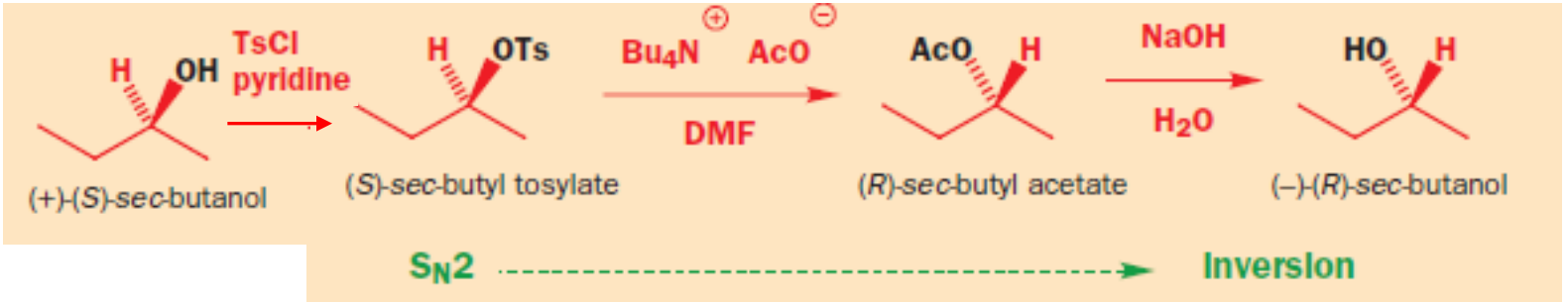


metil- és primer alkilvegyületeknél kizárólagos szubsztitúciós fajta

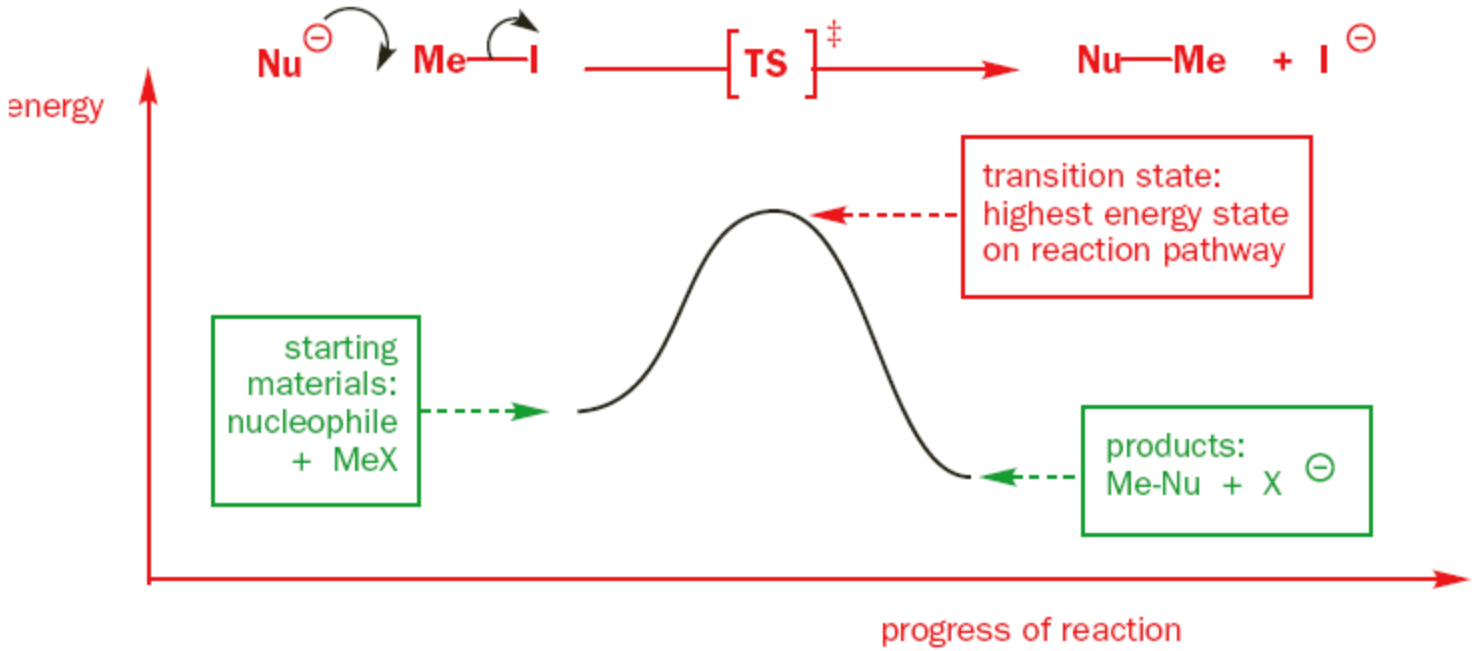



uncluttered approach for nucleophile in $S_N2$ reactions of methyl compounds (R=H) and primary alkyl compounds (R=alkyl)

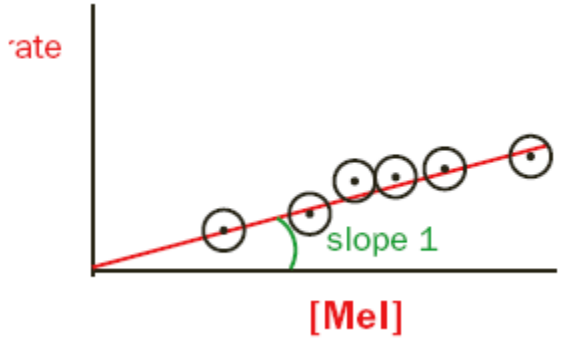
# sztereokémia

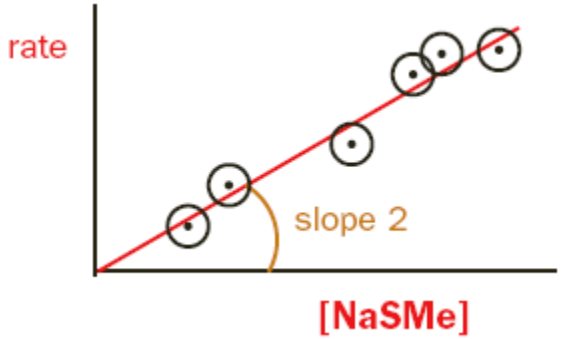


energy diagram for an $S_N2$ reaction



# kinetikai mérés – reakciósebességi egyenlet


If [MeSNa] is constant, the equation becomes

rate = $k_a$[MeI] where $k_a = k_2$[MeSNa]

If [MeI] is constant, the equation becomes

rate = $k_b$[MeSNa] where $k_b = k_2$[MeI]

$$\text{rate} = k_2[\text{MeSNa}][\text{MeI}]$$

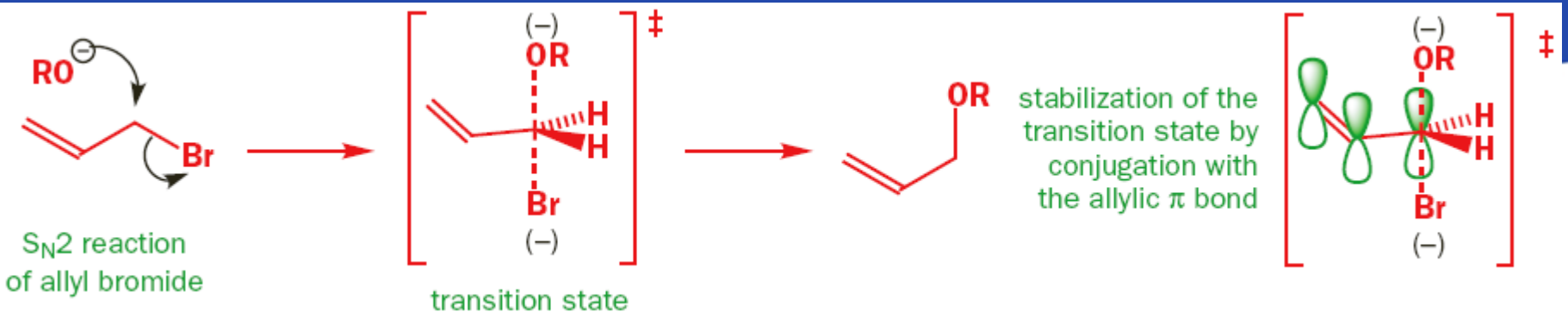
- The rate of an $S_N2$ reaction depends upon:
  - The nucleophile
  - The carbon skeleton
  - The leaving group

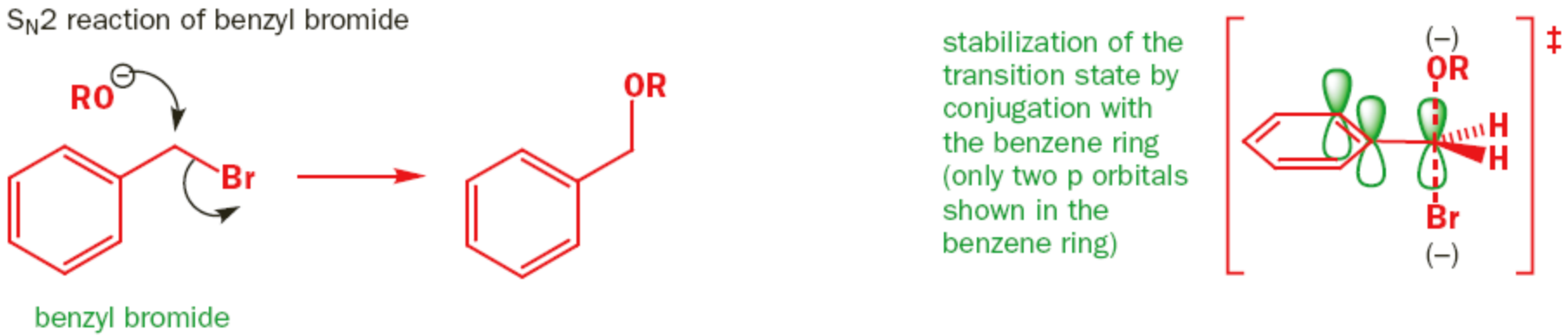
**Table 17.3** Oxygen nucleophiles in the $S_N2$ reaction

| Oxygen nucleophile | p$K_a$ of conjugate acid[a] | Rate in $S_N2$ reaction |
|---|---|---|
| $HO^-$ | 15.7 ($H_2O$) | fast |
| $RCO_2^-$ | about 5 ($RCO_2H$) | reasonable |
| $H_2O$ | –1.7 ($H_3O^+$) | slow |
| $RSO_2O^-$ | 0 ($RSO_2OH$) | slow |

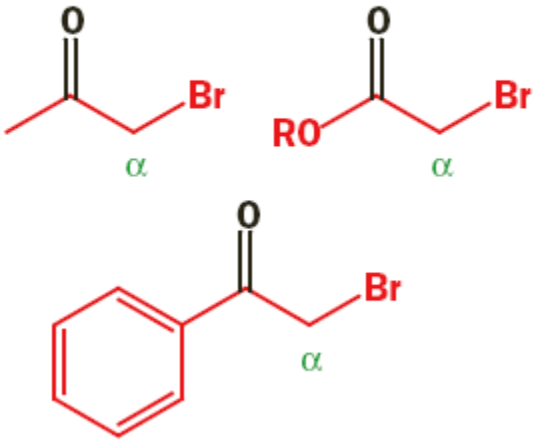
**Table 17.4** Halide leaving groups in the $S_N2$ reaction

| Halide X in MeX | p$K_a$ of conjugate acid HX | Rate of reaction with NaOH |
|---|---|---|
| F | +3 | very slow indeed |
| Cl | –7 | moderate |
| Br | –9 | fast |
| I | –10 | very fast |


RO
Br
SN2 reaction
of allyl bromide
(–)
OR
H
H
Br
(–)
‡
transition state
OR
stabilization of the
transition state by
conjugation with
the allylic π bond
(–)
OR
H
H
Br
(–)
‡

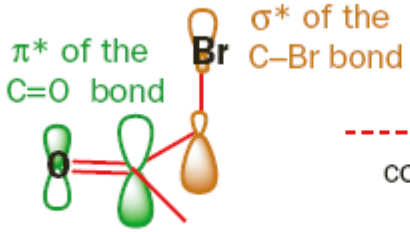

SN2 reaction of benzyl bromide
RO
Br
benzyl bromide
OR
stabilization of the
transition state by
conjugation with
the benzene ring
(only two p orbitals
shown in the
benzene ring)
(–)
OR
H
H
Br
(–)
‡

Reactive α-bromo carbonyl compounds



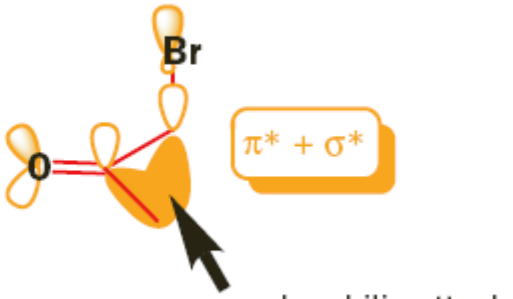

orbitals of:


two LUMOs

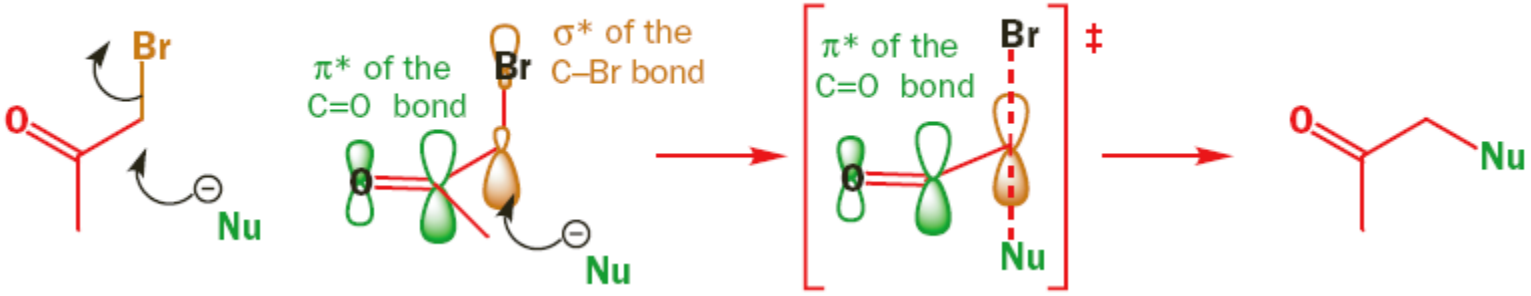



combine

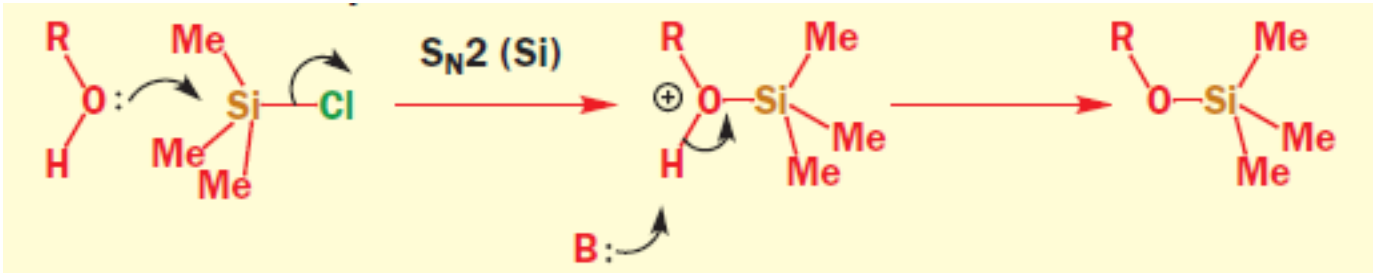
new molecular LUMO

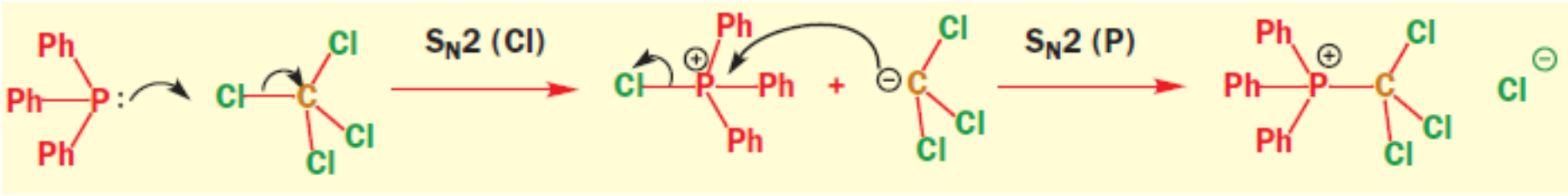



transition state for nucleophilic attack on an α-bromo-ketone

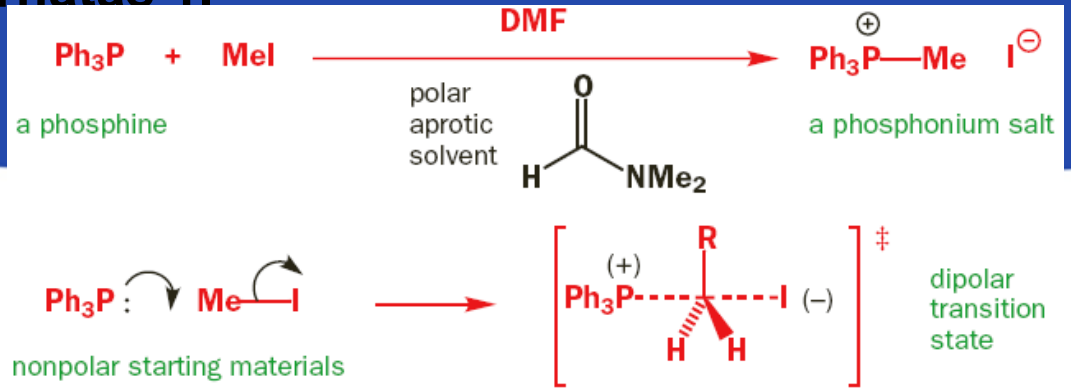


# $S_N2$ reakciók széntől különböző elemeken

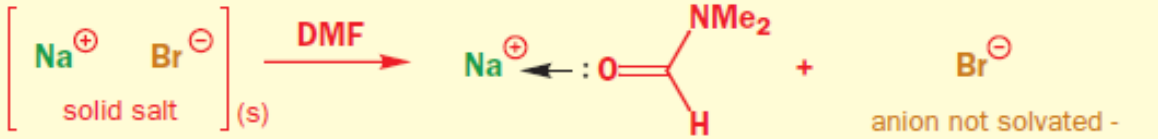


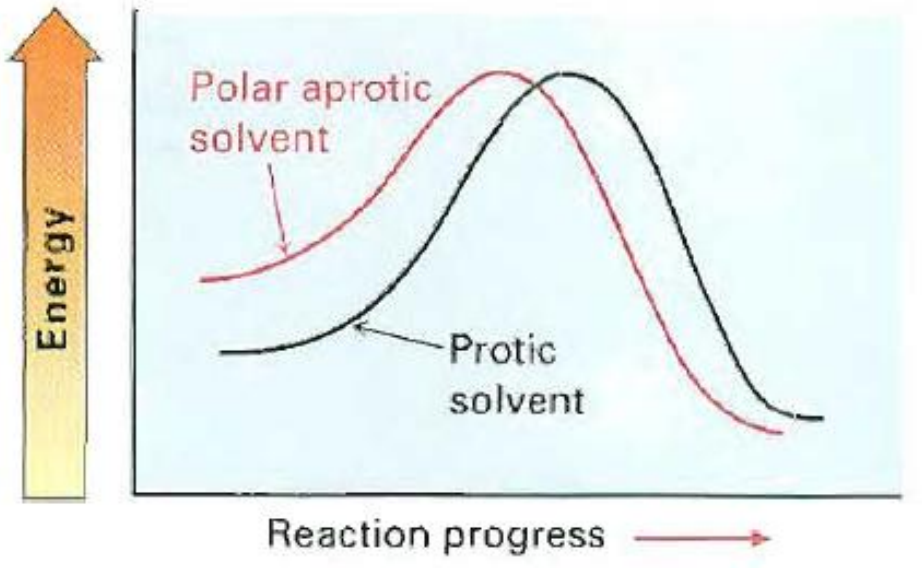



# oldószerhatás 1.

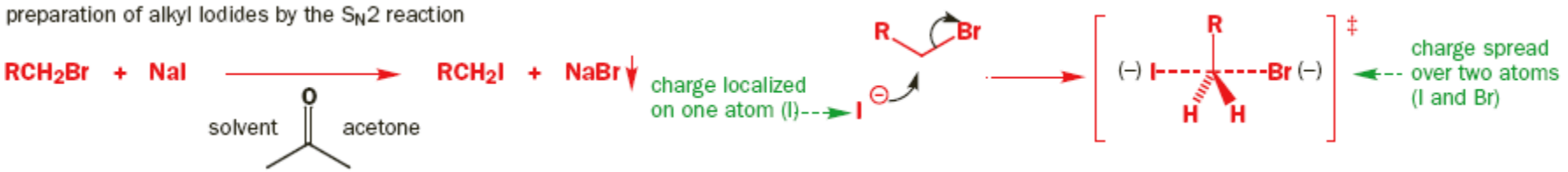



solvation of salts by polar aprotic solvents



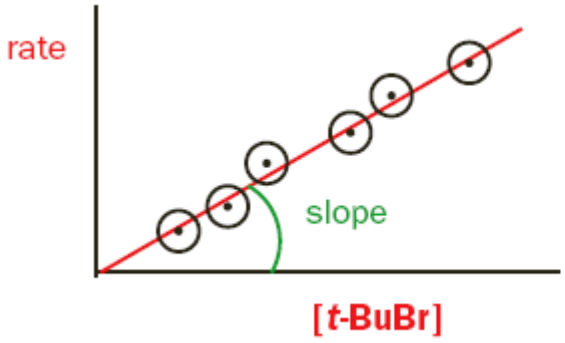



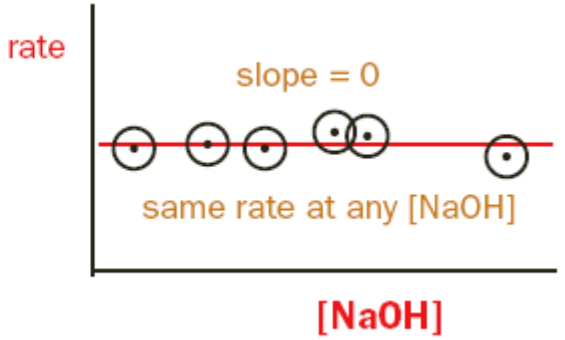
# oldószerhatás 2.




– az aceton kevéssé poláris, így alig szolvatálja a $I^-$-iont, azaz növeli (vagy legalábbis nem csökkenti) reaktivitását
– még kevésbé szolvatálja az átmeneti komplexet, mert a negatív töltés eloszlik
– a NaBr oldhatósága acetonban kisebb, mint a NaI-é

# $S_N1$ reakció

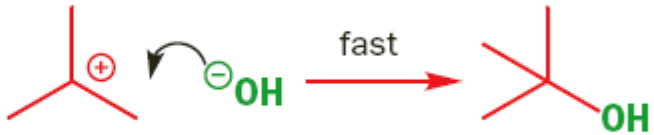




$$\text{rate} = k_1[t\text{-BuBr}]$$

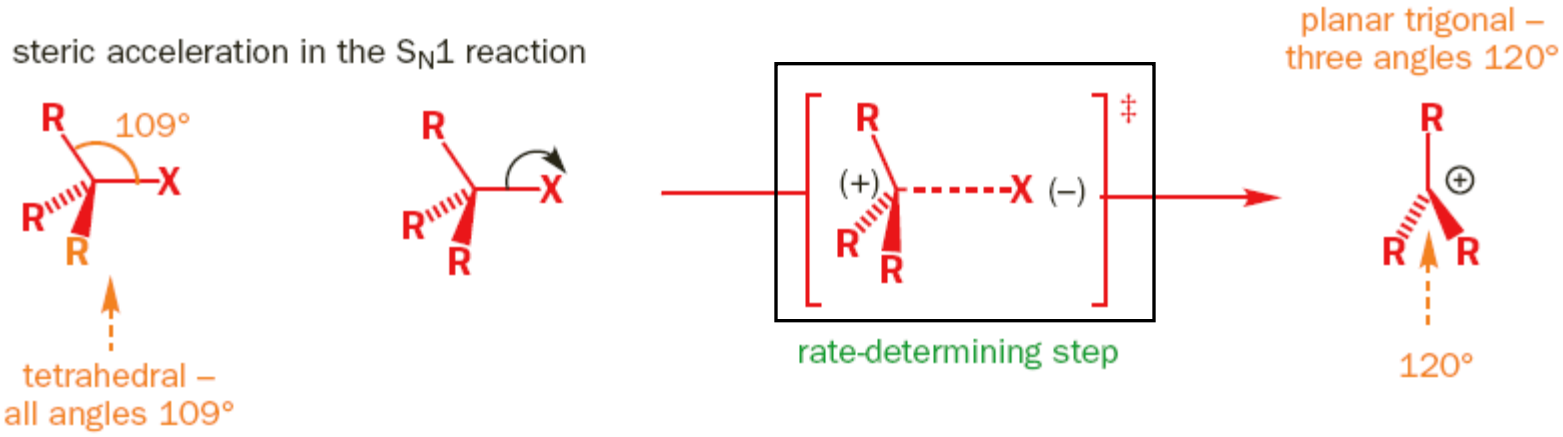
the $S_N1$ mechanism: reaction of *t*-BuBr with hydroxide ion


stage 1: formation of the carbocation




stage 2: reaction of the carbocation

## a mechanizmus az átmeneti állopottal

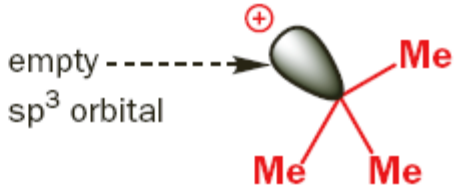


planar structure
for the *t*-butyl cation


correct

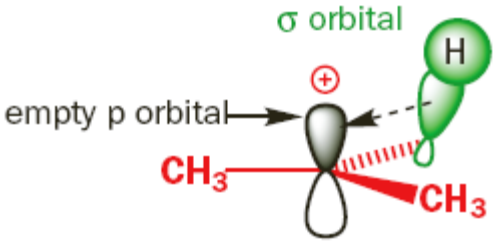
less repulsion between
bonding pairs of electrons

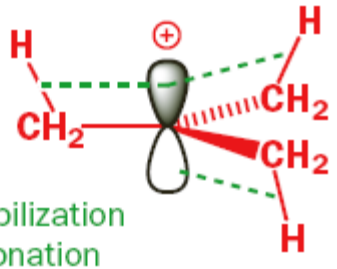
tetrahedral structure
for the *t*-butyl cation



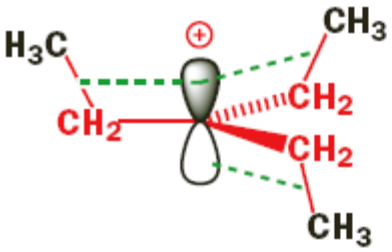

incorrect

more repulsion between
bonding pairs of electrons

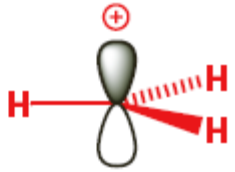



extra stabilization
from σ donation
into empty p orbital
of planar carbocation




extra stabilization
from σ donation
into empty p orbital
of planar carbocation



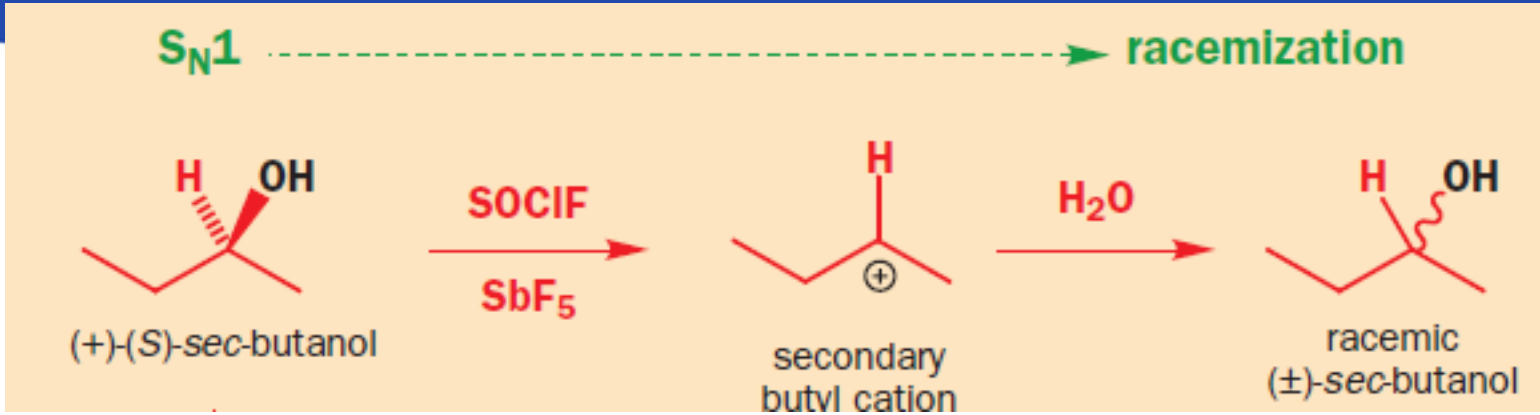

no stabilization: no electrons
to donate into empty p orbital
*note*: The C–H bonds are at
90° to the empty p orbital
and cannot interact with it

hiperkonjugáció

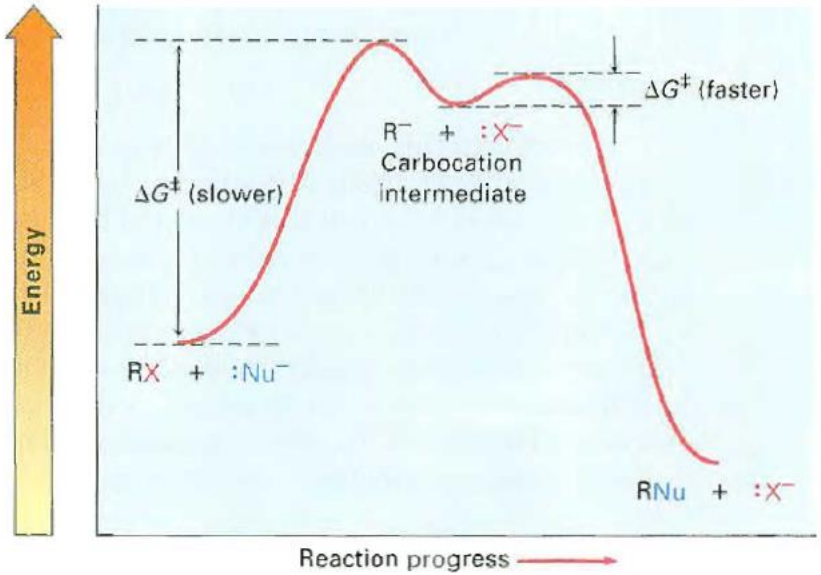

**Table 17.7** Simple structures and choice of $S_N1$ or $S_N2$ mechanism

| structure | Me—X | R, X, H, H | R, X, H, R | R, X, R, R |
|---|---|---|---|---|
| type | methyl | primary | secondary | tertiary |
| $S_N1$ reaction? | no | no | yes | good |
| $S_N2$ reaction? | good | good | yes | no |

# sztereokémia




## az $S_N1$ reakció energiaprofilja

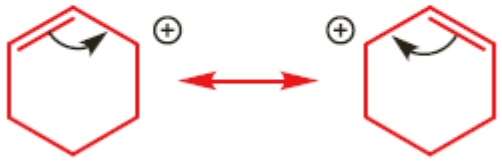


# stabilis kationok, amelyek részt vehetnek $S_N1$ átalakulásokban

the allyl cation

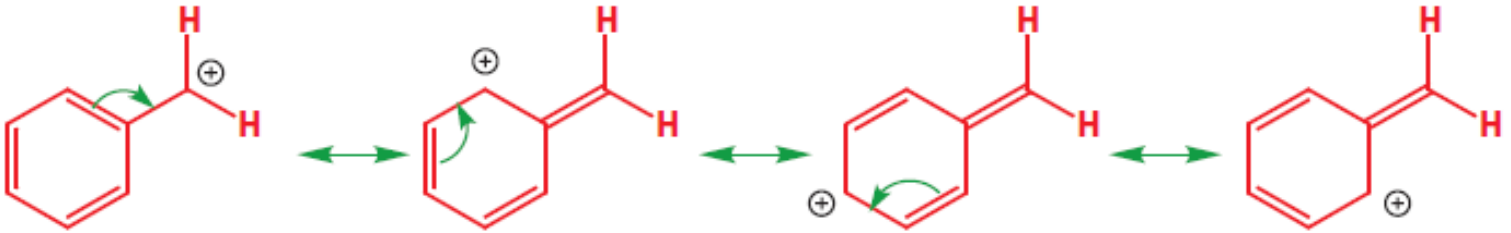
curly arrows

the cyclohexenyl cation



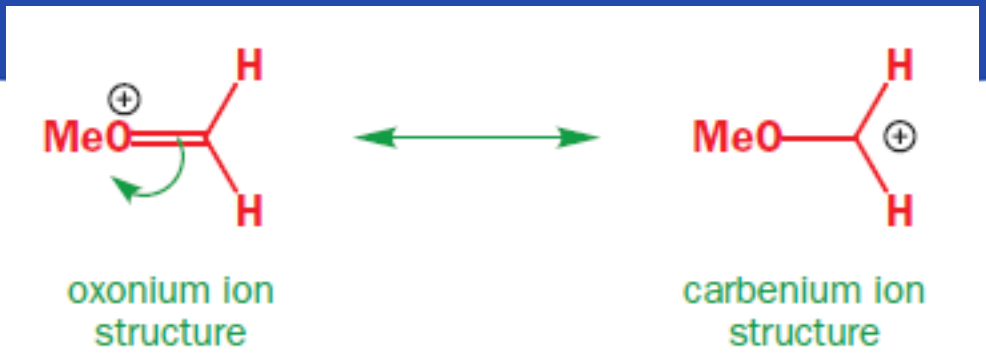
delocalized π bond

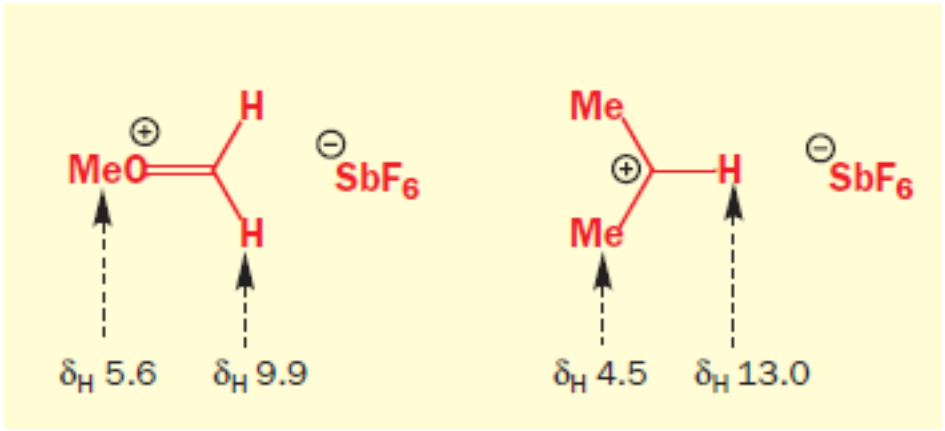
the benzyl cation



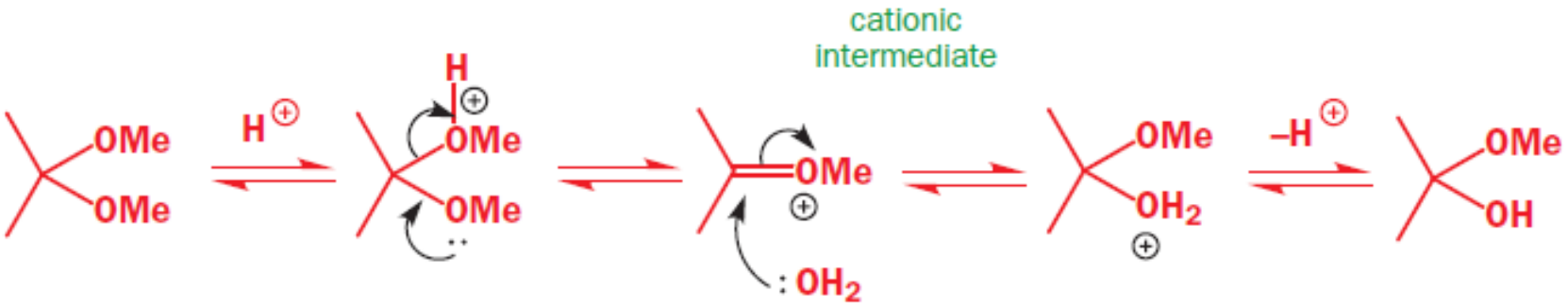

benzylic

# a metoximetil kation

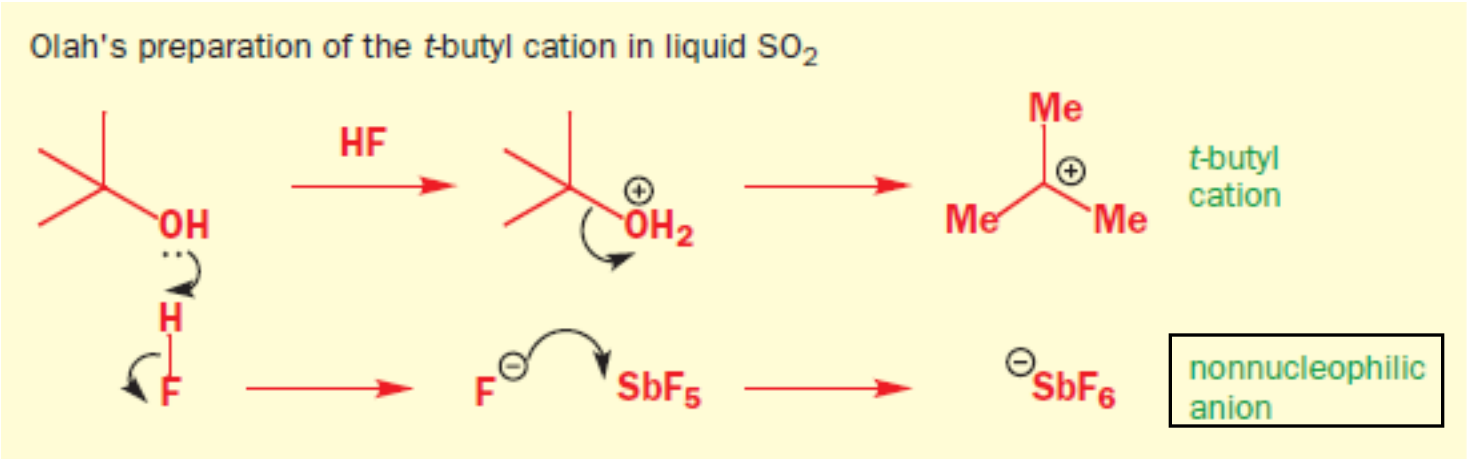



hydrolysis of acetals – $S_N1$ mechanism for the first step



# kationok stabilizálása



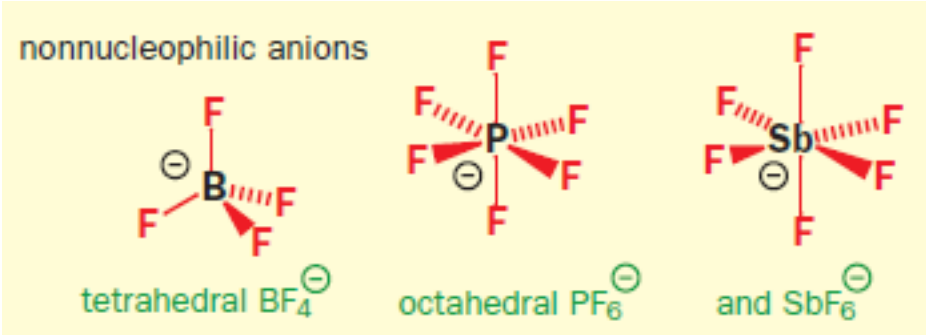
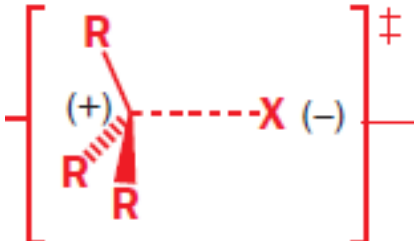



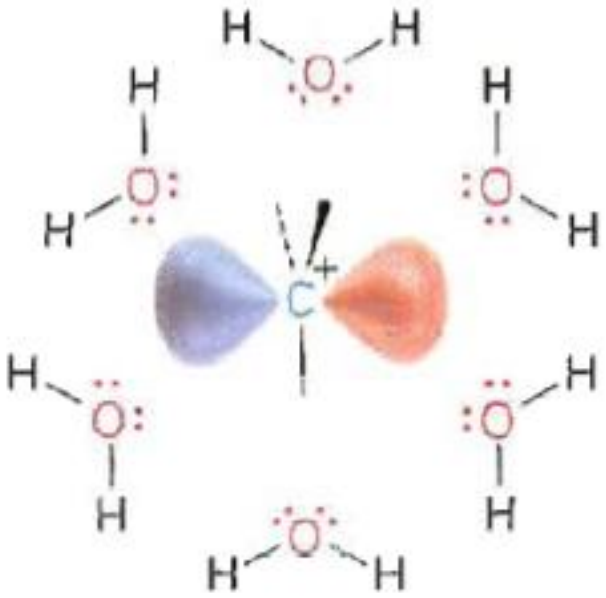
**Table 17.11** Structural variations for the $S_N1$ and $S_N2$ reactions

| Type of electrophilic carbon atom | $S_N1$ reaction | $S_N2$ reaction |
|---|---|---|
| methyl ($CH_3$–X) | no | very bood |
| primary alkyl ($RCH_2$–X) | no | good |
| secondary alkyl ($R_2CH^-X$) | yes | yes |
| tertiary alkyl ($R_3C$–X) | very good | no |
| allylic ($CH_2$=CH–$CH_2$–X) | yes | good |
| benzylic ($ArCH_2$–X) | yes | good |
| α-carbonyl (RCO·$CH_2$–X) | no | excellent |
| α-alkoxy (RO·$CH_2$–X) | excellent | good |
| α-amino ($R_2N$·$CH_2$–X) | excellent | good |

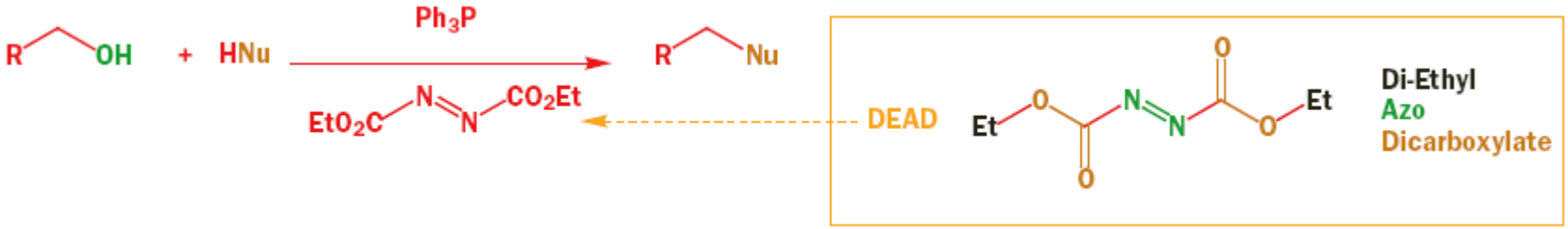
# oldószerhatás

az $S_N1$ reakciót a poláris protikus oldószerek elősegítik, mert szolvatálják az ionos átmeneti komplexet, így csökkentik annak energiáját, azaz a reakció aktiválási energiáját



# Mitsunobu-reakció (OH csere inverzióval – $S_N2$ reakció)



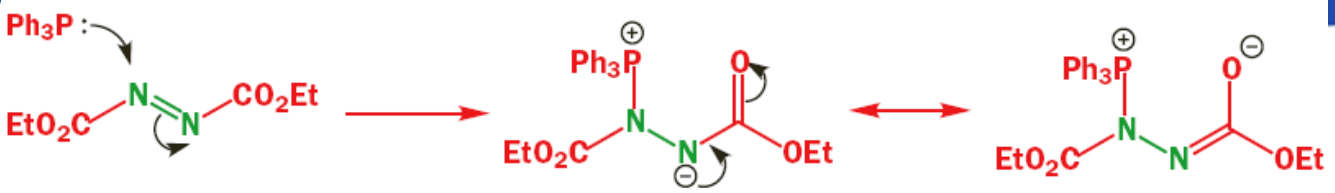

miért hasznos ez a reakció?

az OH–Nu csere általában nehéz, először az OH-csoportot jó távozó csoporttá kell alakítani, a terméket ki kell preparálni, majd ezután mehet a csere

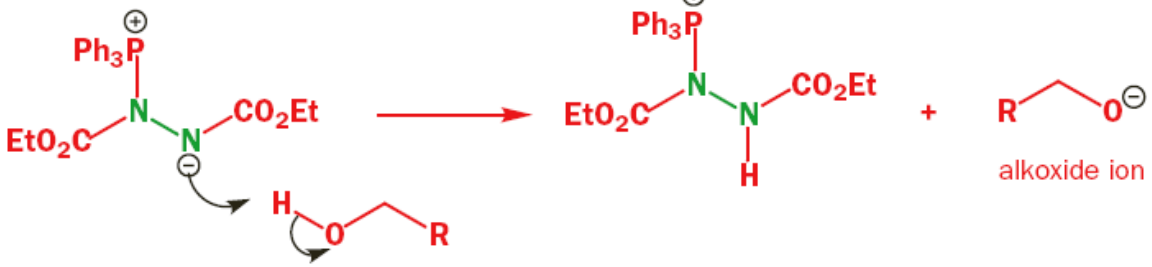
a Mitsunobu-reakció pedig egy edényben lejátszódik (one-pot reaction)

# mechanizmus

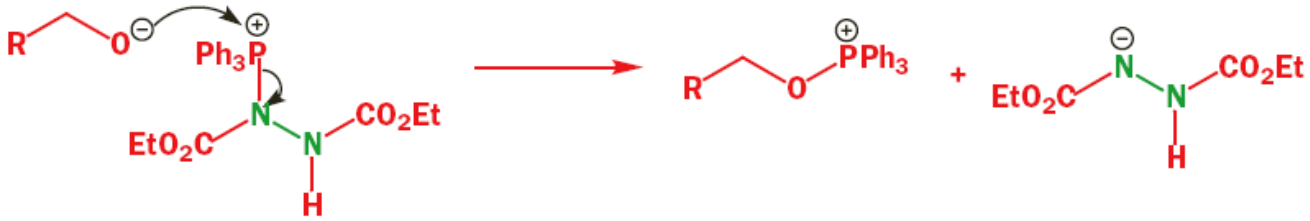
stage 1 of the Mitsunobu reaction




stage 2 of the Mitsunobu reaction

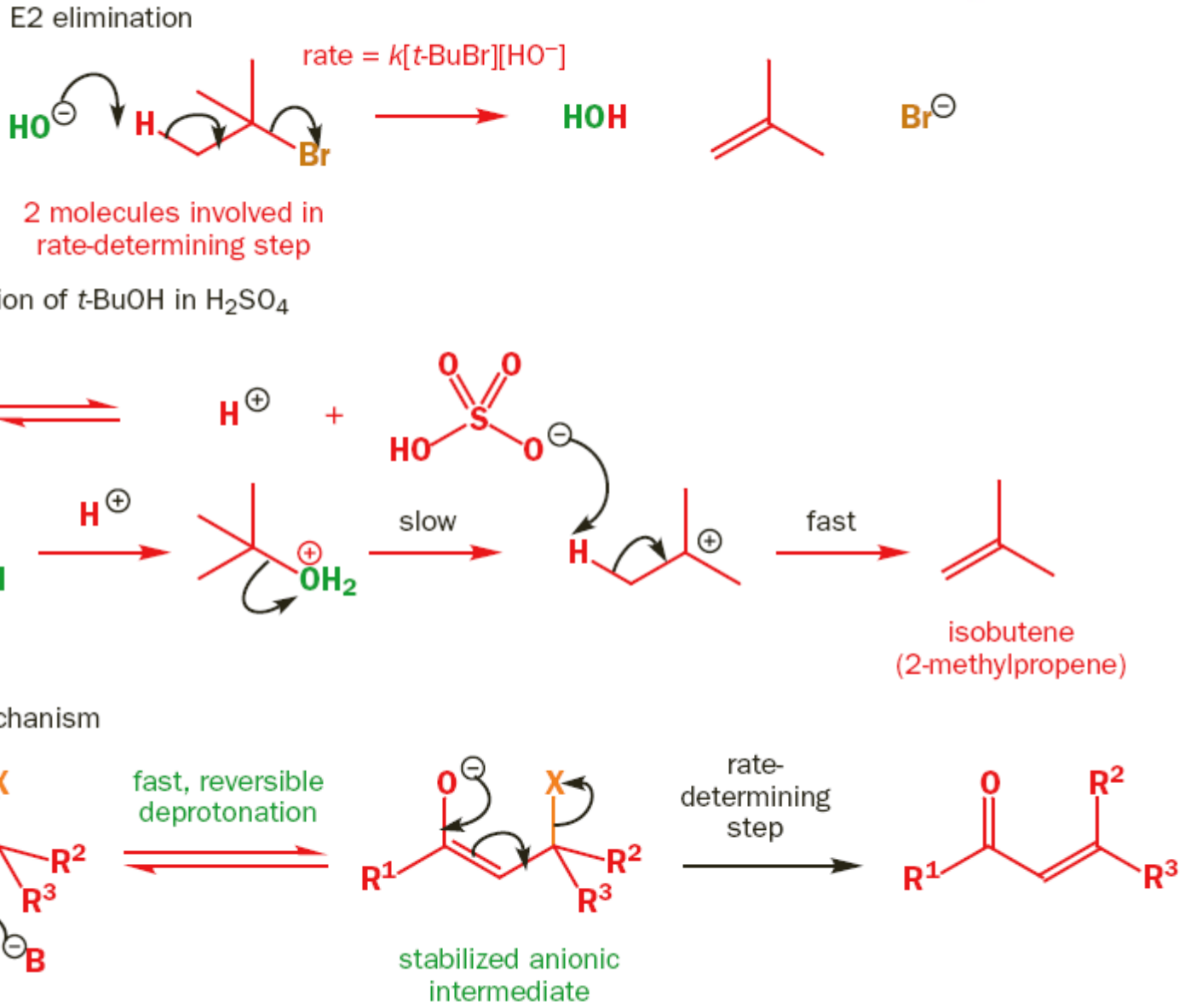



stage 3 of the Mitsunobu reaction




stage 4 of the Mitsunobu reaction

a nukelofil szubsztitúciót gyakran kíséri (akár el is nyomhatja) eliminációtöbb fajtája van:

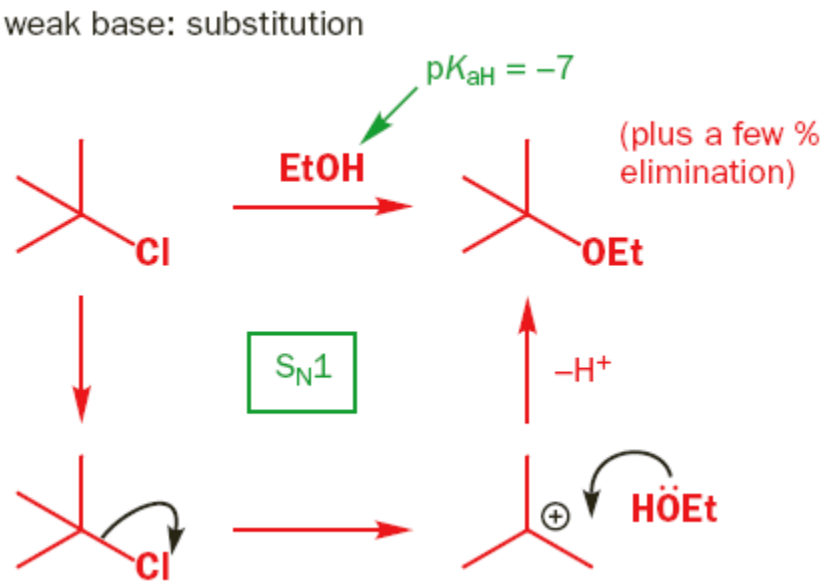


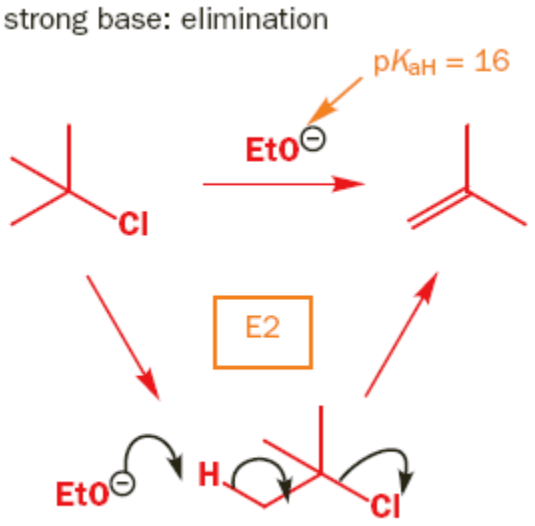
honnan sejthetjük, hogy mikor megy inkább szubsztitúció és mikor elimináció?

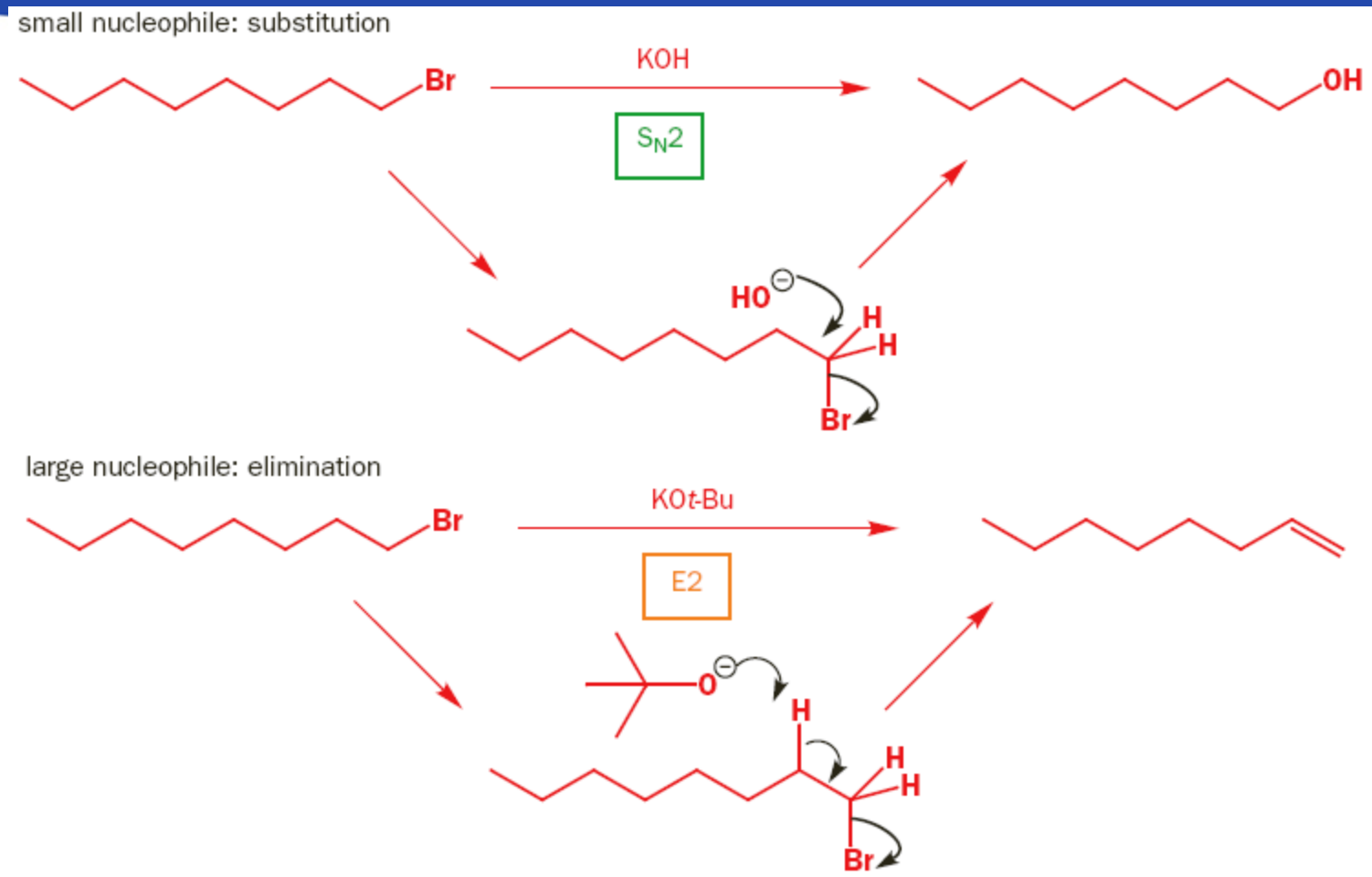
kísérleti tapasztalatok szerint

a magasabb hőmérséklet,
az erősen bázikus kémhatás,
a nagy térkitöltésű nukleofil (bázis)

kedvez az eliminációnak



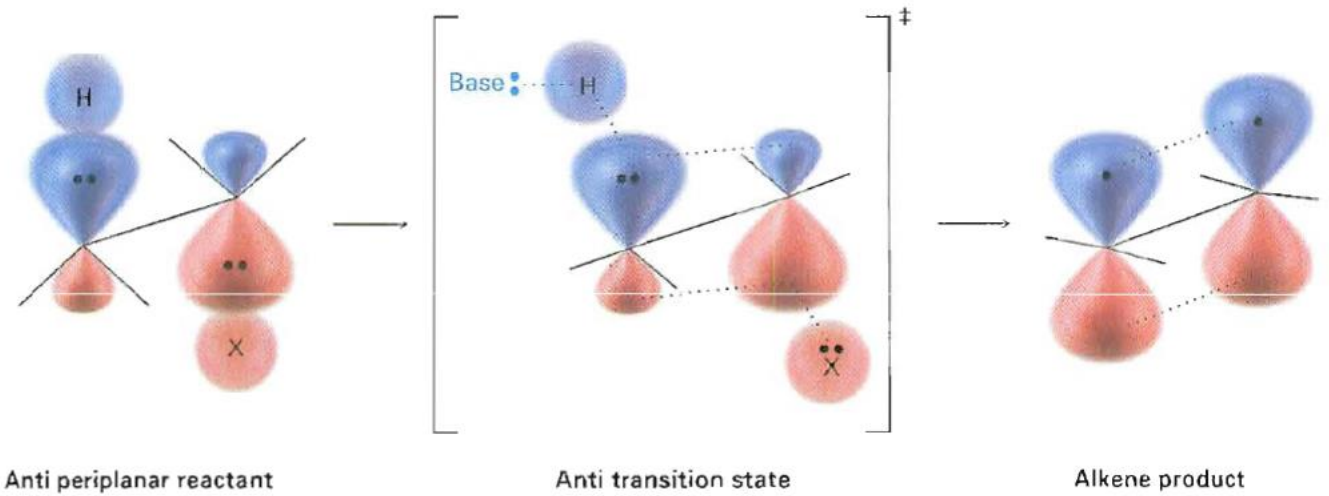

small nucleophile: substitution
Br
KOH
$S_N2$
OH
HO
H
H
Br
large nucleophile: elimination
Br
KO*t*-Bu
E2
O
H
H
H
Br

# E2 (β elimináció)

general mechanism for E2 elimination

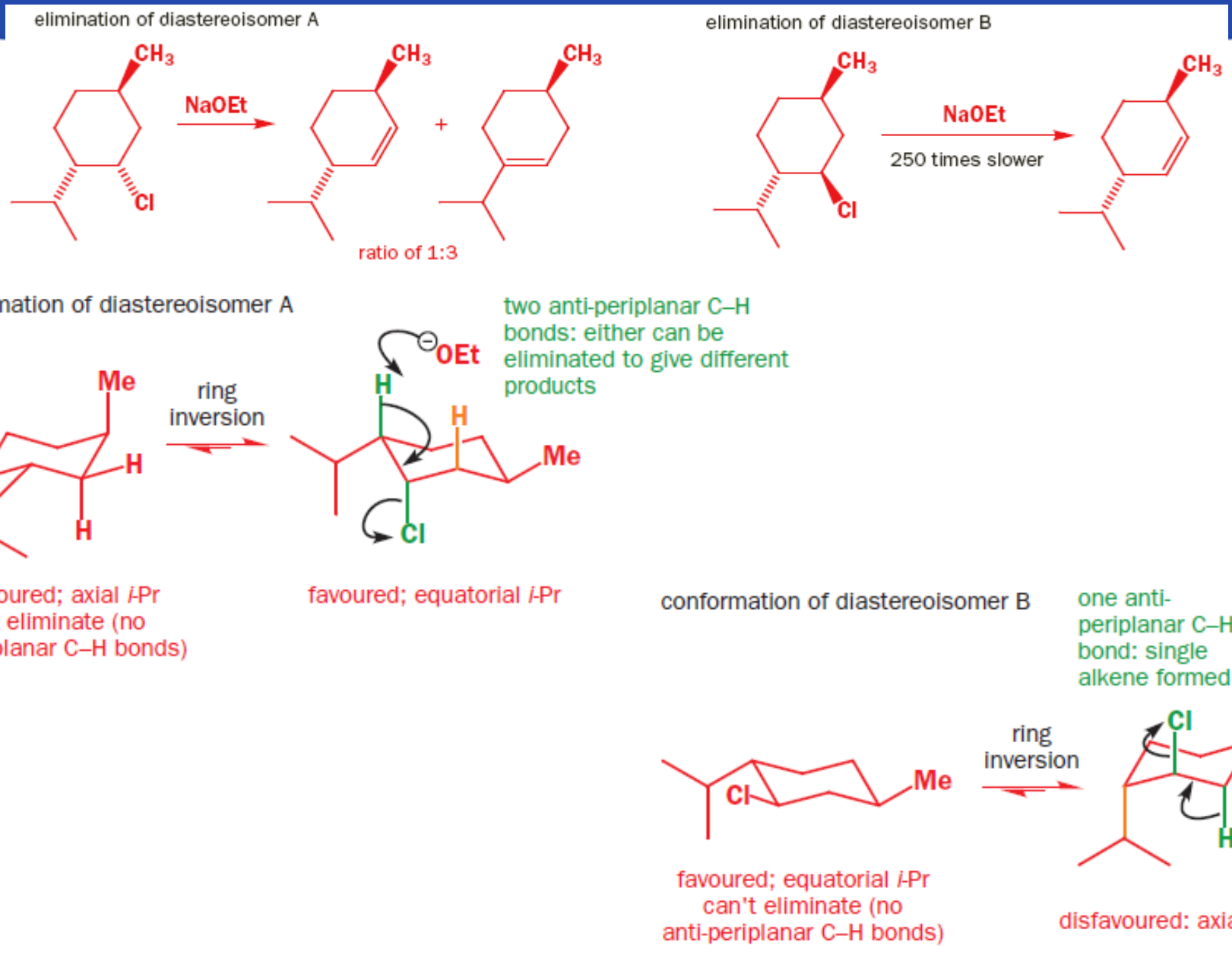
rate = $k[B^-][\text{alkyl halide}]$


az E2 reakció egy koncertikus elemi reakció

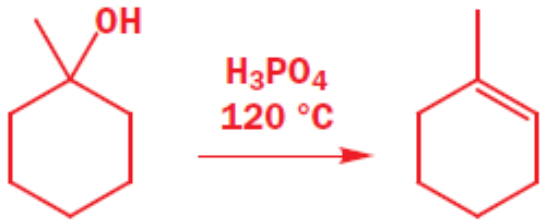



Anti periplanar reactant | Anti transition state | Alkene product

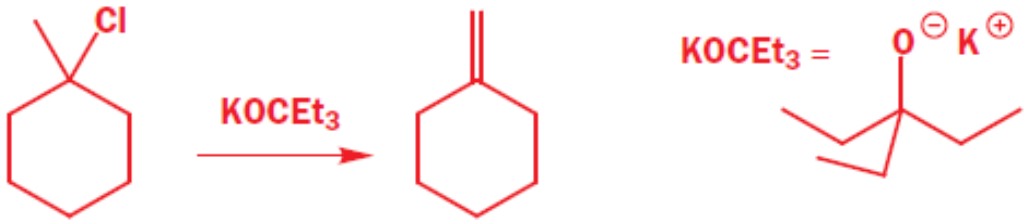
# bizonyíték az antiperiplanáris térállás szükségességére



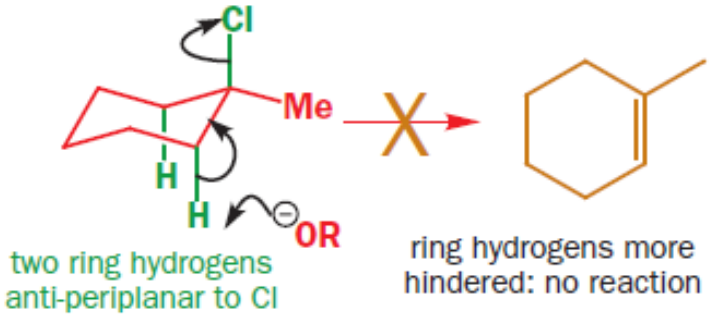
# az E2 reakció régioszelektivitása

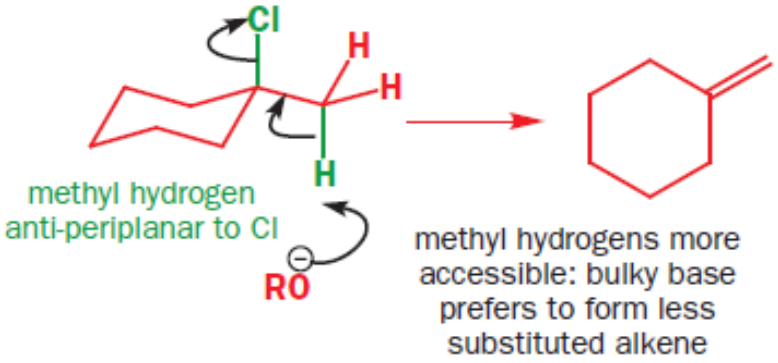



Zajcev-szabály

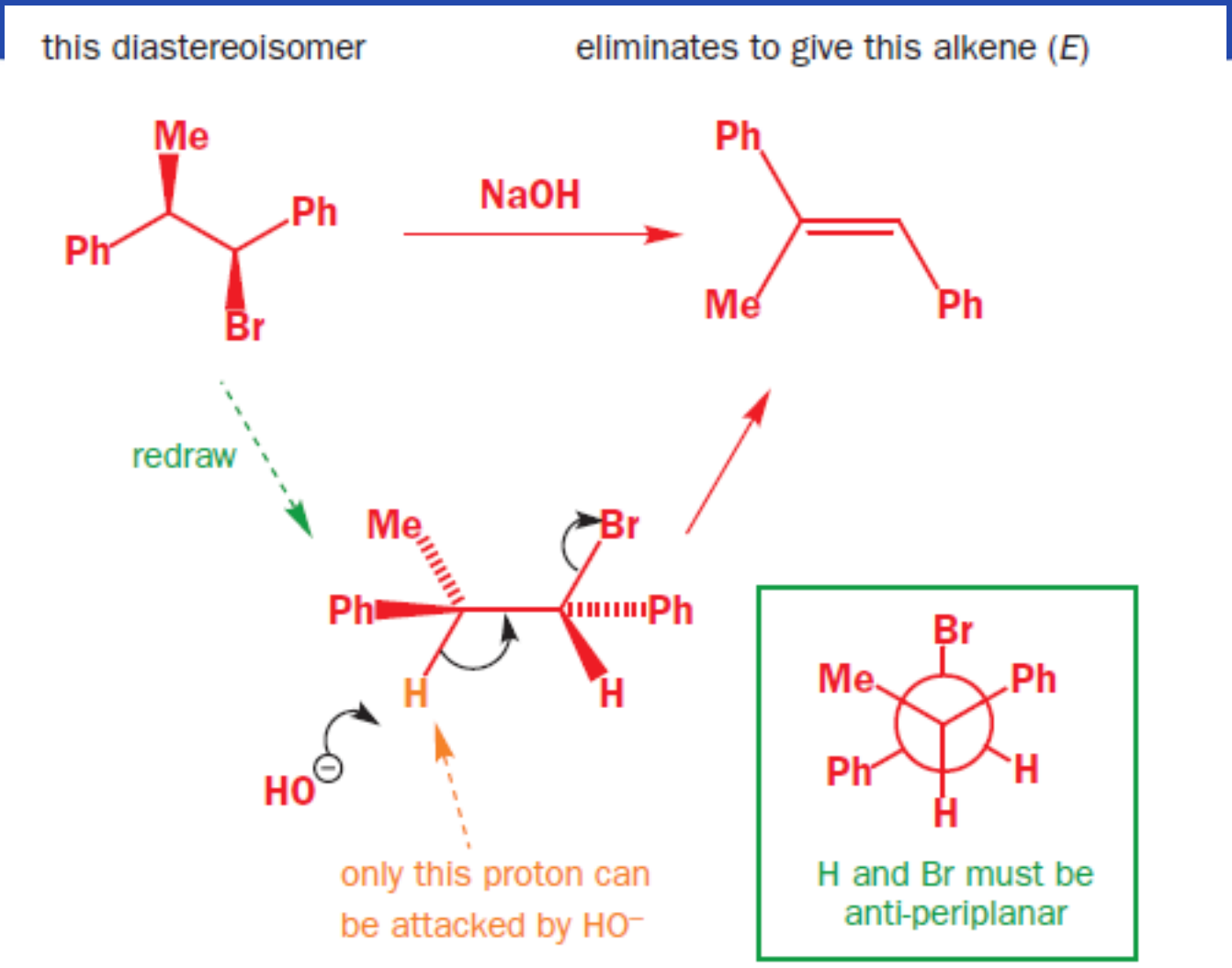



ahogy a költő kérdezné – miért e szívatás?

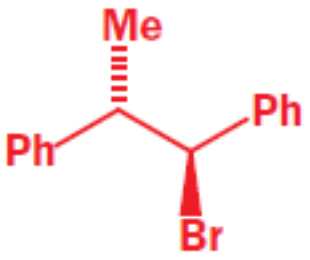


# az E2 reakció lehet sztereospecifikus

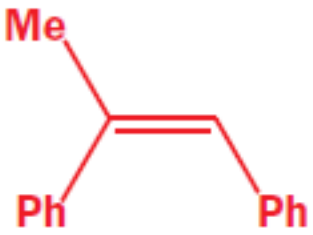


this diastereoisomer

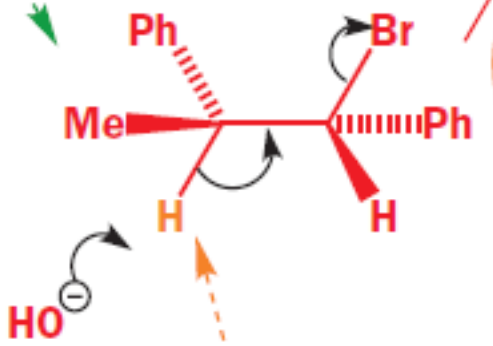



NaOH

eliminates to give this alkene (*Z*)

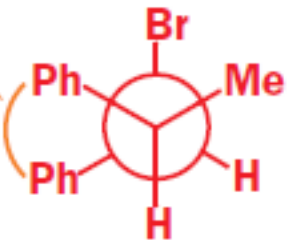



redraw



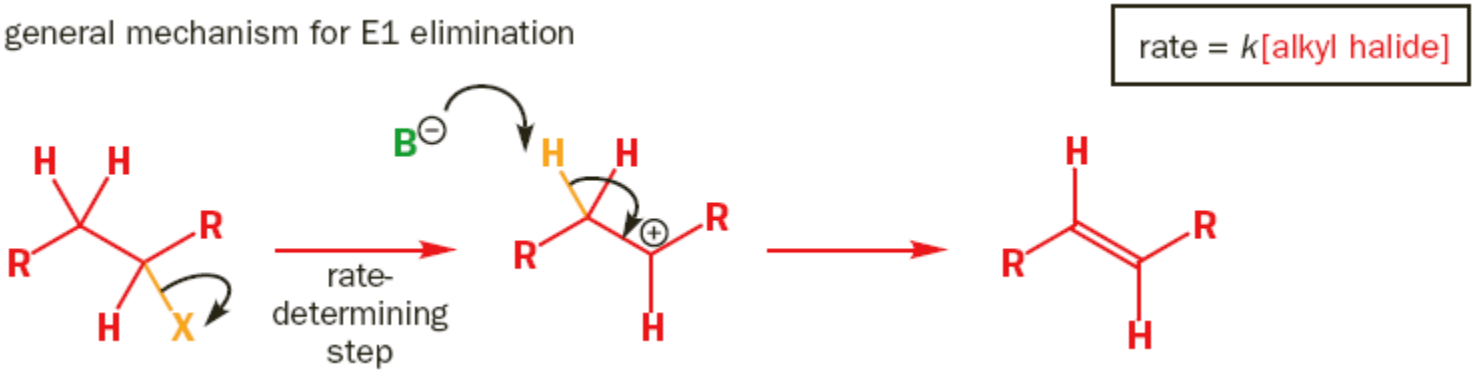

only this proton can be attacked by $HO^-$

slower reaction because of gauche interactions in reactive conformation

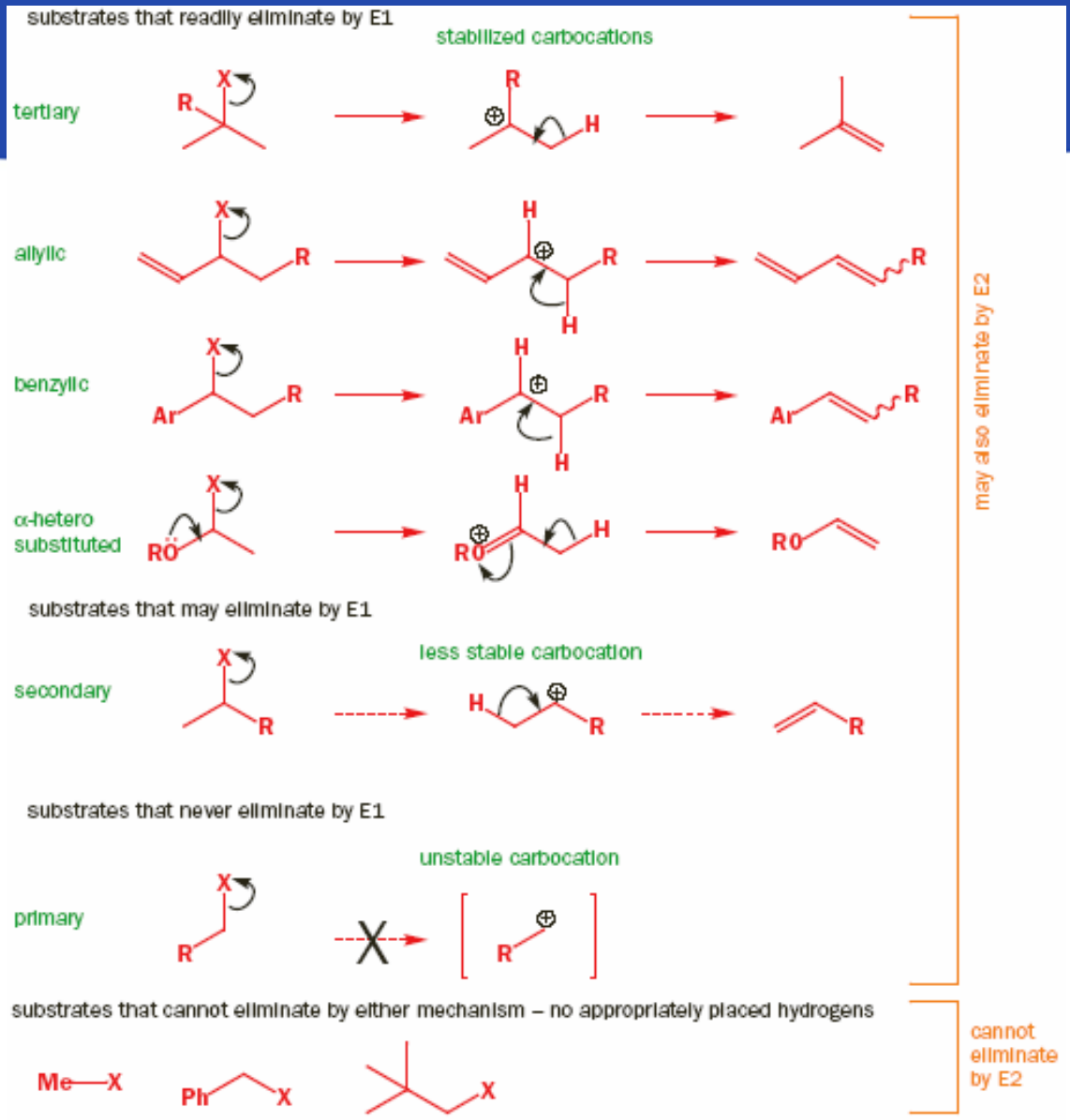



H and Br must be anti-periplanar

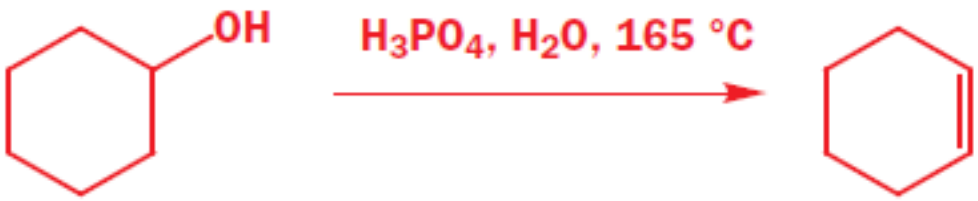
# E1 (β elimináció)



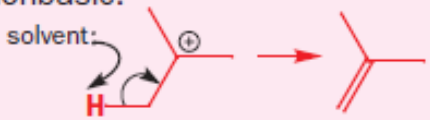

az E1 elimináció összetett reakció, amely két elemi lépésből áll


substrates that readily eliminate by E1
stabilized carbocations
tertiary
allylic
benzylic
α-hetero substituted
substrates that may eliminate by E1
less stable carbocation
secondary
substrates that never eliminate by E1
unstable carbocation
primary
may also eliminate by E2
substrates that cannot eliminate by either mechanism – no appropriately placed hydrogens
cannot eliminate by E2

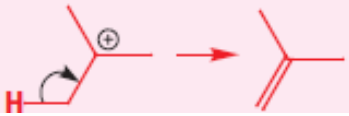
poláris, protikus oldószerekben az E1 mechanizmus kedvezményezett (a karbénium ion intermedier stabilizált)



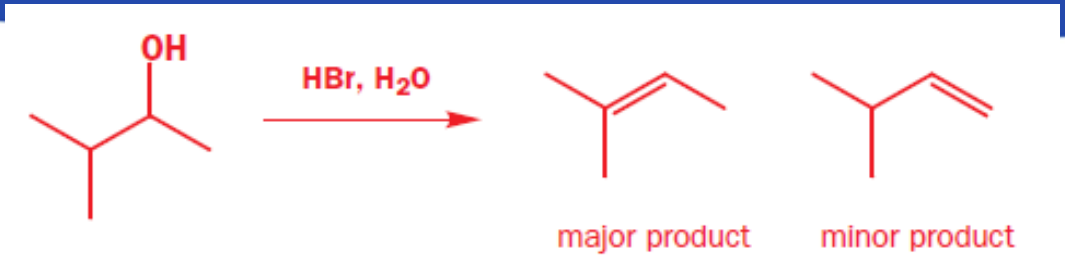

In E1 mechanisms, once the leaving group has departed almost anything will serve as a base to remove a proton from the intermediate carbocation. Weakly basic solvent molecules (water or alcohols), for example, are quite sufficient, and you will often see the proton just 'falling off' in reaction mechanisms. We showed the loss of a proton like this in the last example, and in the chart on p. 000. The superacid solutions we described in Chapter 17 were designed with this in mind—the counterions $BF_4^-$ and $SbF_6^-$ are not only nonnucleophilic but also nonbasic.




is equivalent to

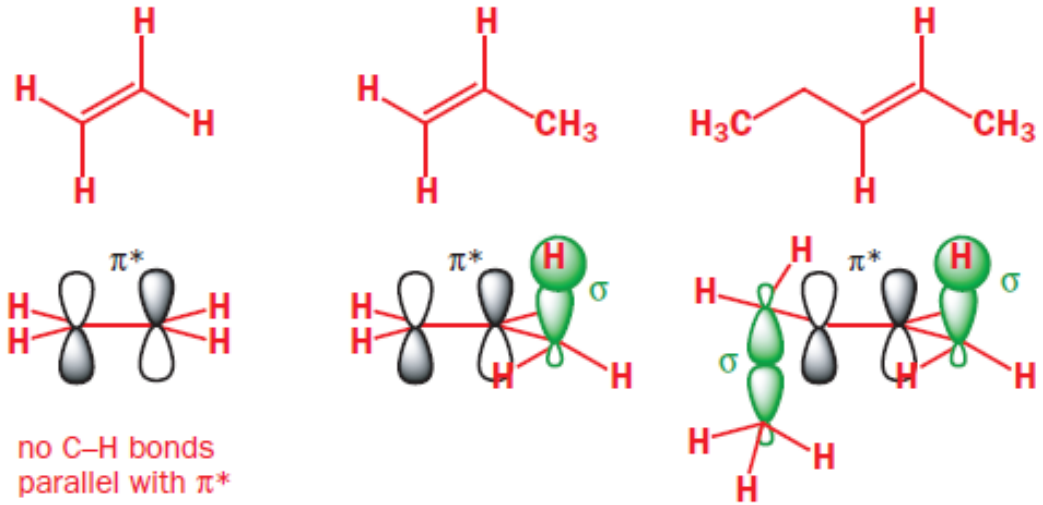


# az E1 reakció régioszelektivitása



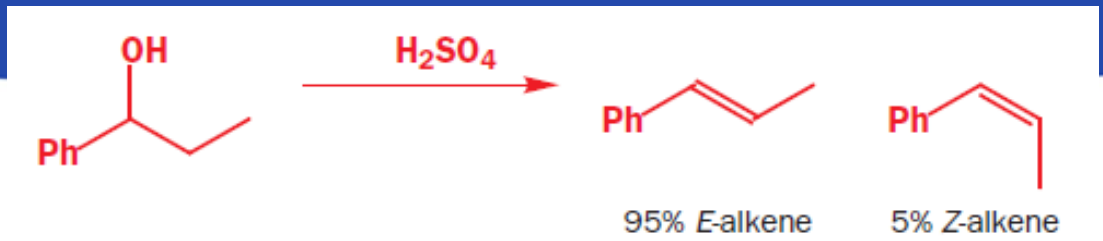

Zajcev-szabály

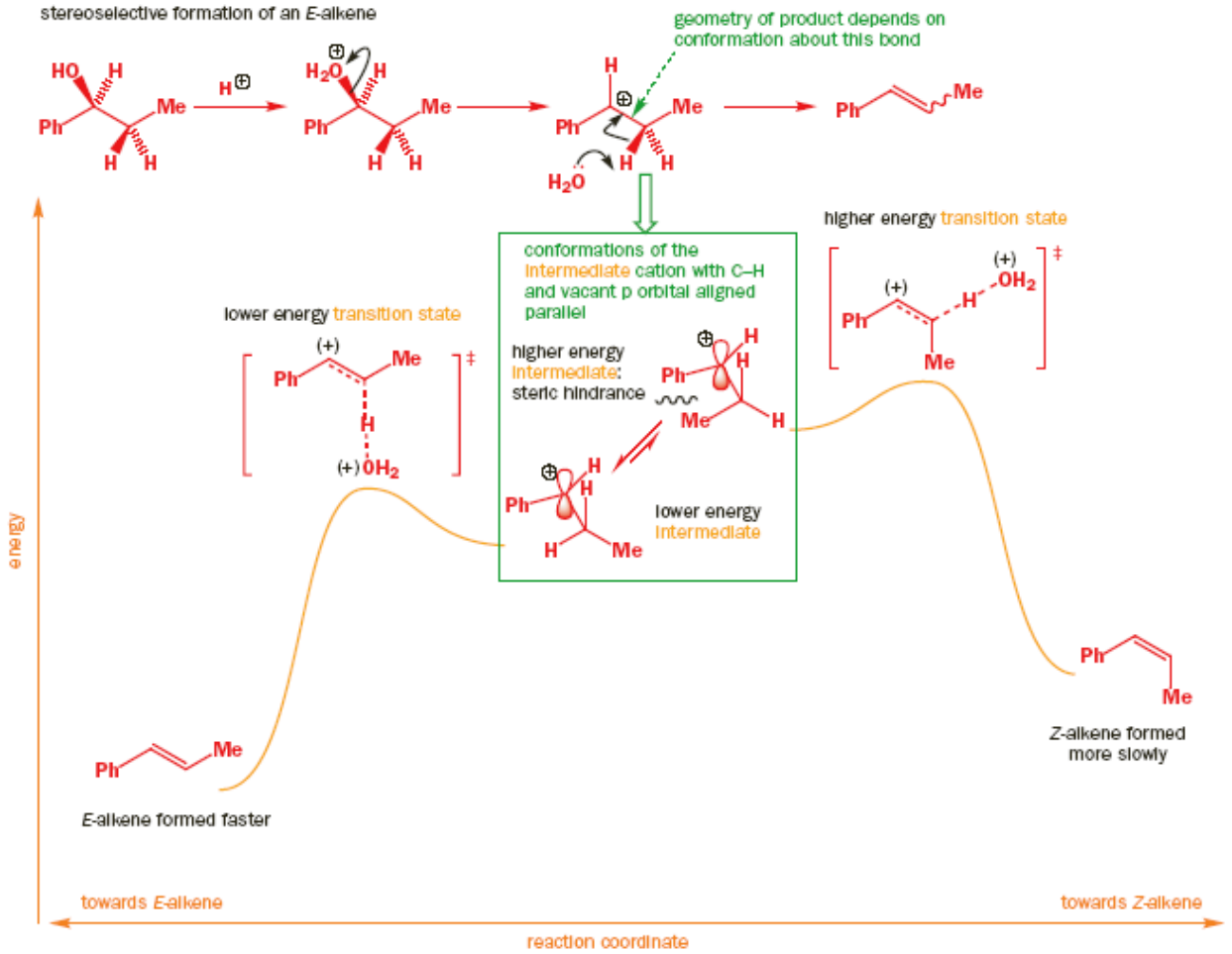
**More substituted alkenes are more stable.**



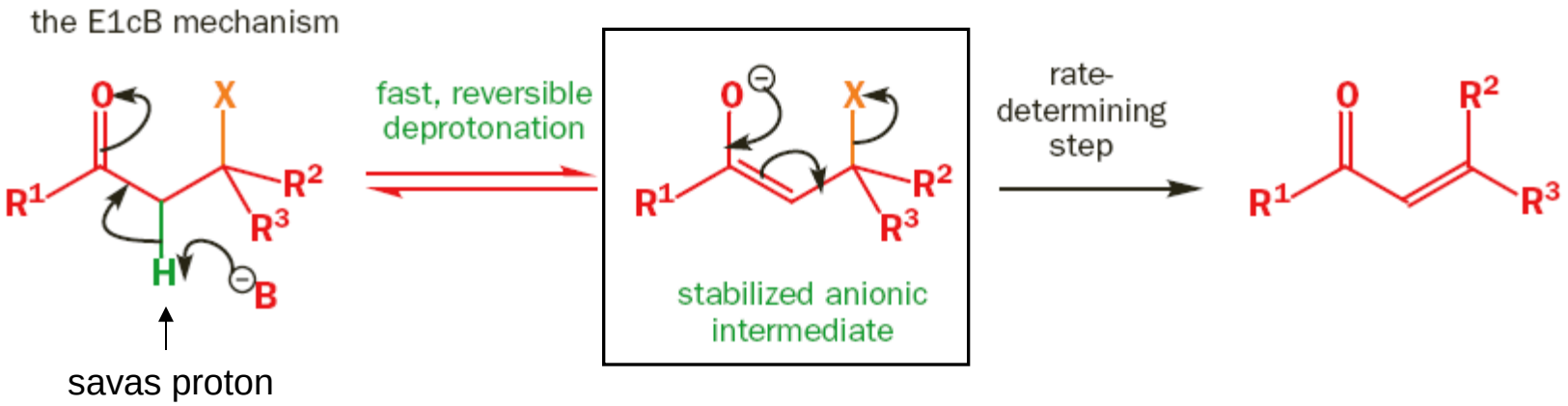

hiperkonjugáció

# az E1 reakció sztereoszelektivitása



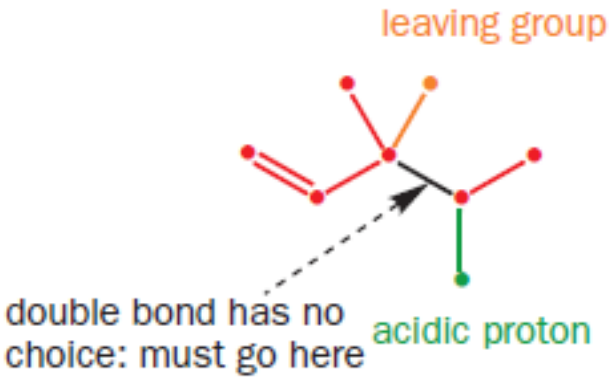



# E1cB (lehet α is)

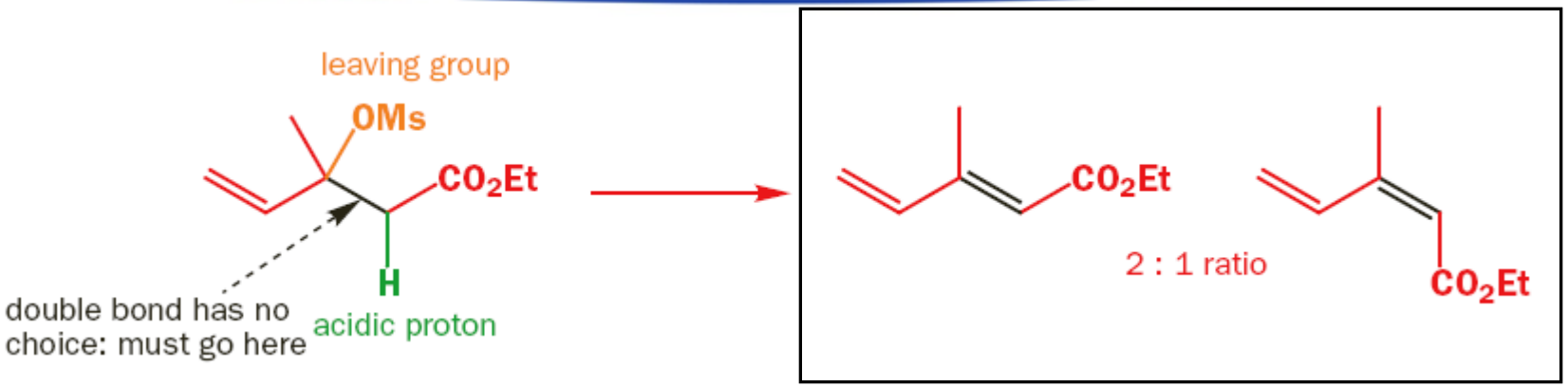


# az E1cB reakció régioszelektivitása

a kettőskötés helyzetét meghatározza a (a) a savas proton és (b) a távozó csoport helyzete



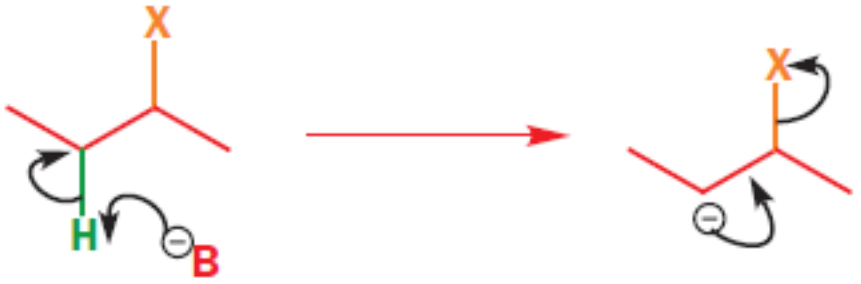
# az E1cB reakció sztereoszelektivitása



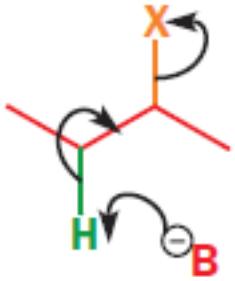

mivel az intermedier anion sík, így a kiindulási vegyület sztereokémiai sajátságai elvesznek – a főtermék a sztérikusan kevésbé gátolt kettőskötésű vegyület lesz

# a három eliminációs mechanizmus összevetése

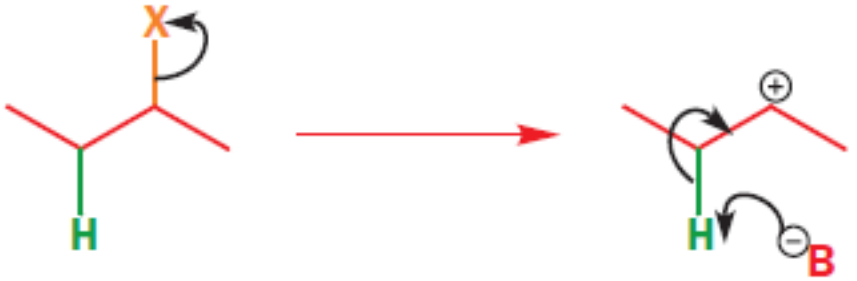
E1cB elimination
deprotonation first
leaving group second



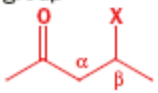

E2 elimination
deprotonation and loss
of leaving group
simultaneous




E1 elimination
leaving group first
deprotonation second



# Összefoglalásul

| | Poor nucleophile (e.g. $H_2O$, ROH)[a] | Weakly basic nucleophile (e.g. $I^-$, $RS^-$) | Strongly basic, unhindered nucleophile (e.g. $RO^-$) | Strongly basic, hindered nucleophile (e.g. DBU, DBN, *t*-$BuO^-$) |
|---|---|---|---|---|
| methyl  | no reaction | $S_N2$ | $S_N2$ | $S_N2$ |
| primary (unhindered)  | no reaction | $S_N2$ | $S_N2$ | E2 |
| primary (hindered)  | no reaction | $S_N2$ | E2 | E2 |
| secondary  | $S_N1$, E1 (slow) | $S_N2$ | E2 | E2 |
| tertiary  | E1 or $S_N1$ | $S_N1$, E1 | E2 | E2 |
| β to anion-stabilizing group  | E1cB | E1cB | E1cB | E1cB |

[a] Acid conditions.

# KÖSZÖNÖM A FIGYELMET!

SZÉCHENYI 2020

MAGYARORSZÁG KORMÁNYA

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