CHEM 221 section 01

LECTURE #22 Thurs., Nov.17, 2005

ASSIGNED READINGS:

TODAY'S CLASS: **Up to 10.8**

NEXT LECTURE: **finish Ch.10 after lab exam**

http://artsandscience.concordia.ca/facstaff/P-R/rogers

The Effect of Solvent on Nucleophilicity

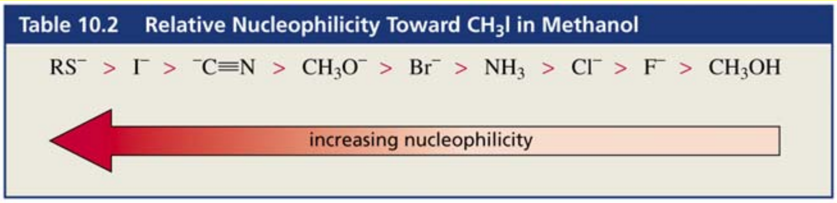


Table 10.2 Relative Nucleophilicity Toward CH_3I in Methanol

$RS^- > I^- > {}^-C{\equiv}N > CH_3O^- > Br^- > NH_3 > Cl^- > F^- > CH_3OH$

increasing nucleophilicity

How does a protic solvent make strong bases less nucleophilic?

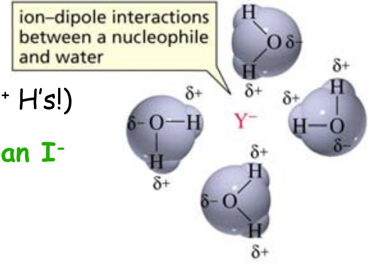
"Protic solvents":
= organic solvents with OH or NH groups *i.e.,* H-bond donors

Nucleophile's lone pairs become "distracted" (attack δ^+ C's less) by interacting with the δ^+ H's of highly polar solvents!

→ happens more with "harder", stronger bases…
→ weaker, "softer" (more polarizable) bases interact less with H's

Solvent effect: consider the ion–dipole interaction…

- Easier to break the ion-dipole interactions between a *weaker base* and the solvent than between a ***stronger base*** and the solvent (since stronger bases interact better with δ^+ H's!)



Example: F^- is not really a better Nu than I^-

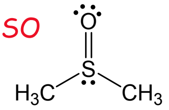
- Fluoride = a relatively strong "weak base"
  ∴ only a good Nu in nonpolar solvents
- Iodide = an incredibly weak "weak base"
  ∴ always a good Nu!

Application: aprotic polar solvents (not H-bond donors) facilitate rxn of **ionic compounds** because they solvate cations

→ pull cations away from incoming Nu^-

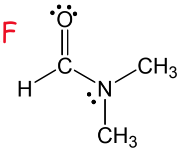
→ makes Nu^- more "naked" & reactive to δ^+ Cs

DMSO



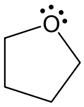
dimethylsulfoxide

DMF



dimethylformamide

THF



tetrahydrofuran

NUCLEOPHILE STRENGTH IN HYDROXYLIC (PROTIC) SOLVENTS (SUCH AS WATER & ALCOHOLS)

STRONG nucleophiles	MODERATE nucleophiles	WEAK nucleophiles
$(CH_3CH_2)_3P:$	$:\ddot{Br}:^{\ominus}$	$:\ddot{F}:^{\ominus}$
$^{\ominus}:\ddot{S}-H$	$:NH_3$	$H-\ddot{O}-H$
$^{\ominus}:C\equiv N:$	$CH_3-\ddot{S}-CH_3$	$CH_3-\ddot{O}-H$
$(CH_3CH_2)_2\ddot{N}H$	$:\ddot{Cl}:^{\ominus}$	REMEMBER: Nu concentration is also important… if lots is present, rxn WILL occur!
$^{\ominus}:\ddot{O}-H$		
$^{\ominus}:\ddot{O}-CH_3$	$CH_3\overset{\overset{\ddot{O}}{\|}}{C}-\ddot{O}:^{\ominus}$	

SUMMARY OF TRENDS IN NUCLEOPHILICTY

1. A species with a negative charge is a stronger nucleophile than a similar neutral species. In particular, a base is a stronger nucleophile than its conjugate acid.

   $OH^- > H_2O$ $SH^- > H_2S$ $NH_2^- > NH_3$

2. Nucleophilicity decreases from left to right in the periodic table (based on attacking atom), following the increase in electronegativity from left to right. The more electronegative elements have more tightly held nonbonding electrons (lone pairs) that are less reactive towards forming new bonds.

   $OH^- > F^-$ $NH_3 > H_2O$ $(CH_3CH_2)_3P > (CH_3CH_2)_2S$

3. Nucleophilicity increases down the periodic table, following the increase in size and polarizability.

   $I^- > Br^- > Cl^- > F^-$ $^-SeH > {}^-SH > {}^-OH$ $(CH_3CH_2)_3P > (CH_3CH_2)_3N$

From Wade LJ, Organic Chemistry, 5th Ed.

10.4 S_N2 reactions are equilibria (reversible rxns!) Which direction dominates?

An S_N2 reaction proceeds (net) in the direction that allows the strongest base to displace the weaker base

$CH_3CH_2Cl + HO^- \longrightarrow CH_3CH_2OH + Cl^-$
an alcohol

$CH_3CH_2Br + HS^- \longrightarrow CH_3CH_2SH + Br^-$
a thiol

$CH_3CH_2I + RO^- \longrightarrow CH_3CH_2OR + I^-$
an ether

$CH_3CH_2Br + RS^- \longrightarrow CH_3CH_2SR + Br^-$
a thioether

$CH_3CH_2Cl + {}^-NH_2 \longrightarrow CH_3CH_2NH_2 + Cl^-$
a primary amine

$CH_3CH_2Br + {}^-C{\equiv}CR \longrightarrow CH_3CH_2C{\equiv}CR + Br^-$
an alkyne

$CH_3CH_2I + {}^-C{\equiv}N \longrightarrow CH_3CH_2C{\equiv}N + I^-$
a nitrile

PREDICTING DIRECTION:
The group that gets displaced more often is the one that is better able to carry its charge (the weaker base)

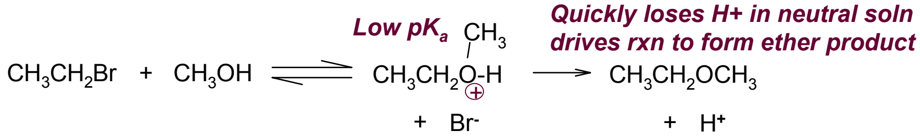
THIS IS USEFUL:
- can predict products!
- use substitution rxns to prepare interesting compounds from alkyl halides!
- since an eqm, can drive rxn in 1 direction by removing product…

Not only alkyl halides: All of this applies to compounds containing other leaving groups

Compare pK_as of conjugate acids of common leaving groups
⇨ convenient for predicting rxn's preferred direction
⇨ AND NOTE: not all leaving groups are ANIONS

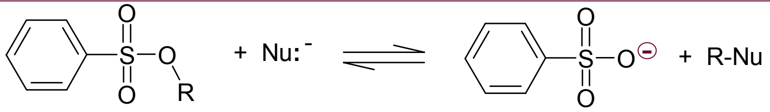
- protonated alcohols: H_2O can leave
- protonated ethers: ROH can leave
- protonated amines: NH_3 can leave

See Table 10.3



Low pK_a

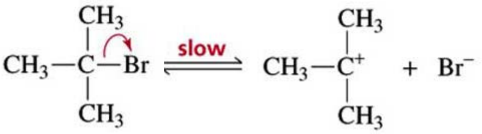
Quickly loses H+ in neutral soln drives rxn to form ether product



Tosylate "OTs" fantastic leaving group
HOTs pK_a ~ -0.6 (very strong conj. acid)

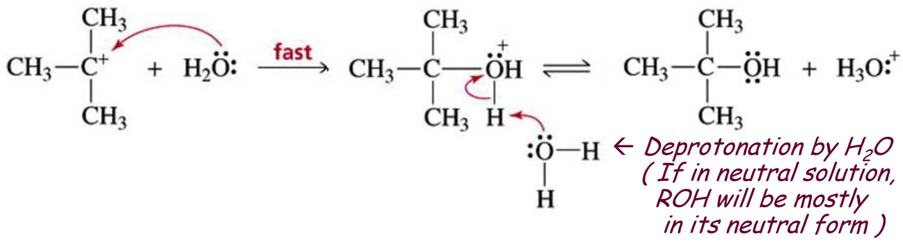
10.5 The mechanism of an S_N1 reaction

Carbocation ⇨ open shell ⇨ <u>HIGHLY</u> electrophilic !



⇐ RATE-LIMITING STEP

- stable molecule falls apart!
- rxn shows 1st order kinetics
- rate = *k* [alkyl halide]

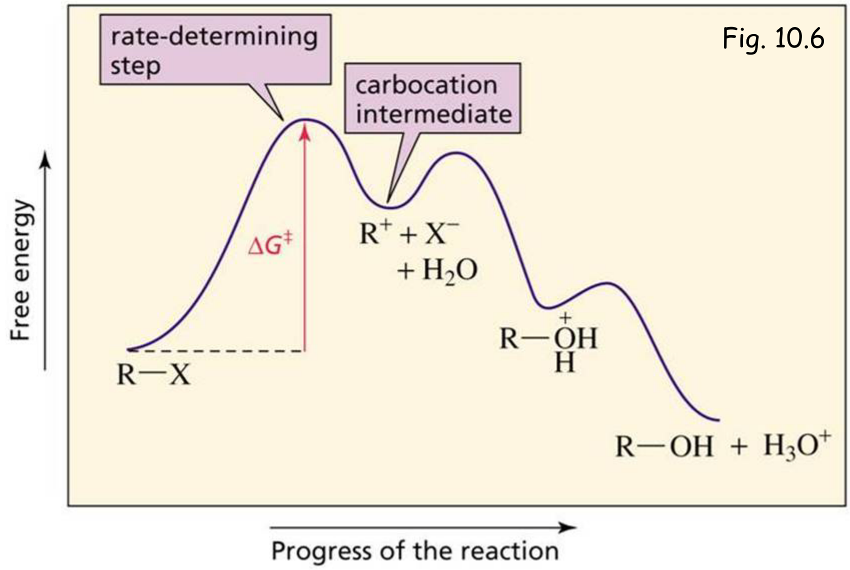


← Deprotonation by H_2O (If in neutral solution, ROH will be mostly in its neutral form)

"SUBSTITUTION NUCLEOPHILIC UNIMOLECULAR" = "S_N1"
└ RLS involves only 1 molecule

1st step (SLOW): LG leaves (heterolytic C-X bond cleavage)
2nd step (FAST): Nu attacks carbocation intermediate
& Possibly more steps: often see H^+ transfer to/from solvent

Reaction Coordinate Diagram for an S_N1 Reaction



Experimental evidence for substitution occurring via an S_N1 mechanism

1. The rate of the reaction depends only on the concentration of the alkyl halide (*i.e.,* not on [Nu])
   → heterolytic C-X cleavage occurs <u>before</u> Nu attack

2. The reaction is faster for halides with bulkier alkyl substituents
   → because of increased stability of carbocation intermediate
   → inductive stabilization by R groups, same as for radicals!
   → also: sterically blocks reactive C+ centre ⇨ slows down LG re-attacking carbocation (1st step in reverse)

3. In the substitution of a chiral alkyl halide, a racemic mixture of product is obtained
   → this mechanism is NOT stereospecific
   → because Nu can attack either side of planar carbocation !

10.6 Factors affecting S_N1 reactions: LG & Nu

The Effect of the Leaving Group on an S_N1 Reaction

most reactive > RI > RBr > RCl > RF < least reactive

- Better leaving group ⇨ more probable C-X cleavage (= RLS!)
  ⇨ faster S_N1 rxn! *(but it's always quite slow)*

WHY? → better LGs (weaker bases) are less tightly held by C
__Not__ restricted to halides; don't forget other types of LG

The Effect of the Nucleophile on an S_N1 Reaction ?

The strength of the nucleophile has <u>no effect</u> on the rate of an S_N1 reaction, because the Nu is <u>not involved in the RLS</u> *(as long as it can collide with the carbocation & provide a lone pair to the C+ centre, the carbocation will be rapidly consumed as it forms)*

- solvolysis = reaction with a solvent
  often <u>the solvent</u> is the Nu in S_N1 reactions
  → *"rescues"* carbocations that occasionally form via C-X cleavage!

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Steric effects: bulkier alkyl halides have increased rate of heterolytic cleavage to form carbocation (= RLS for S_N1)

most reactive > 3° alkyl halide > 2° alkyl halide > 1° alkyl halide < least reactive

opposite trend compared to S_N2 rxns!

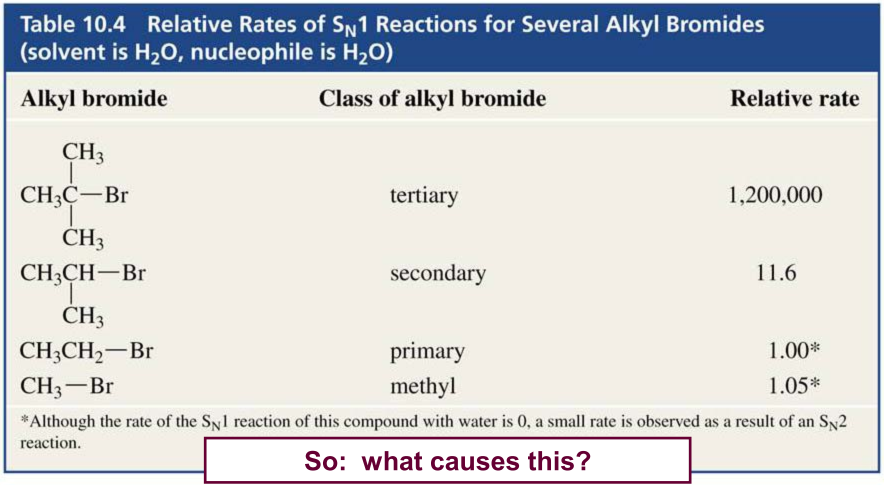


Table 10.4 Relative Rates of S_N1 Reactions for Several Alkyl Bromides (solvent is H_2O, nucleophile is H_2O)

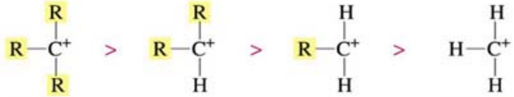
Alkyl bromide	Class of alkyl bromide	Relative rate
$CH_3\overset{CH_3}{\underset{CH_3}{C}}-Br$	tertiary	1,200,000
$CH_3\underset{CH_3}{CH}-Br$	secondary	11.6
CH_3CH_2-Br	primary	1.00*
CH_3-Br	methyl	1.05*

*Although the rate of the S_N1 reaction of this compound with water is 0, a small rate is observed as a result of an S_N2 reaction.

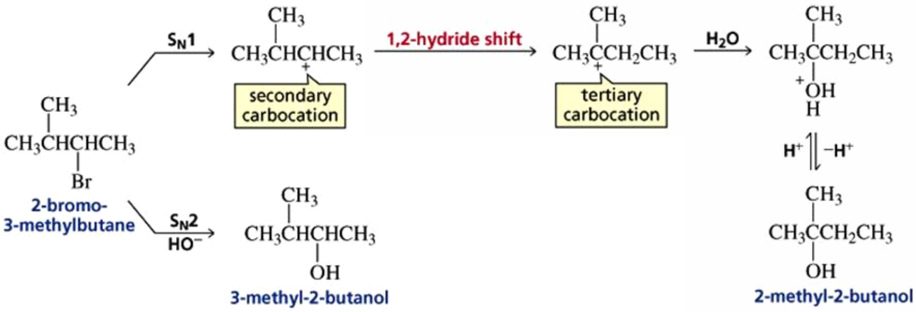
So: what causes this?

Stability of carbocation intermediate: more stable? ⇨ forms faster!

Remember:
Alkyl groups stabilize carbocations via
1. inductive e^- donation
2. hyperconjugation



Always remember to check for possible rearrangements:



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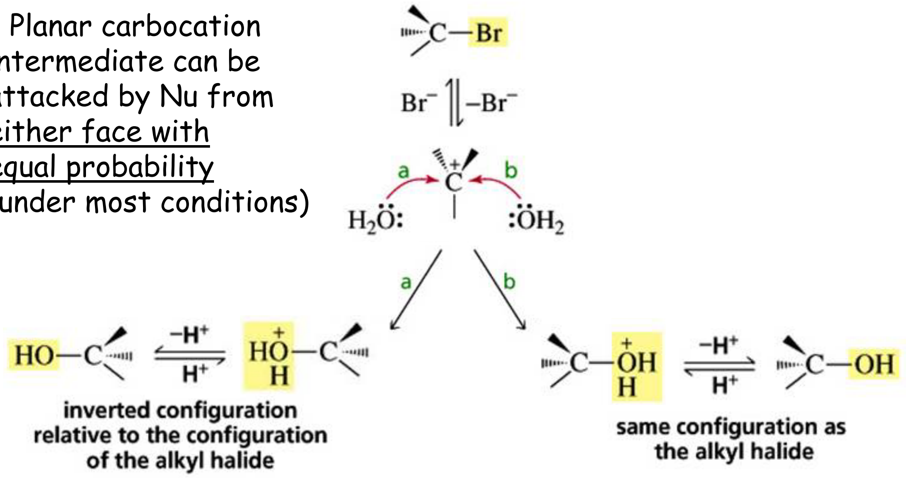
10.7 Stereochemistry of S_N1 reactions

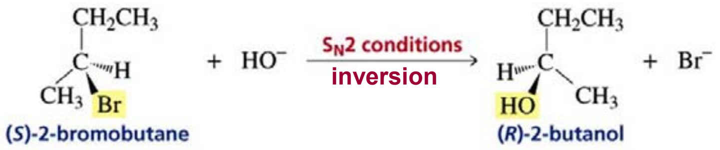
- Planar carbocation intermediate can be attacked by Nu from <u>either face with equal probability</u> (under most conditions)

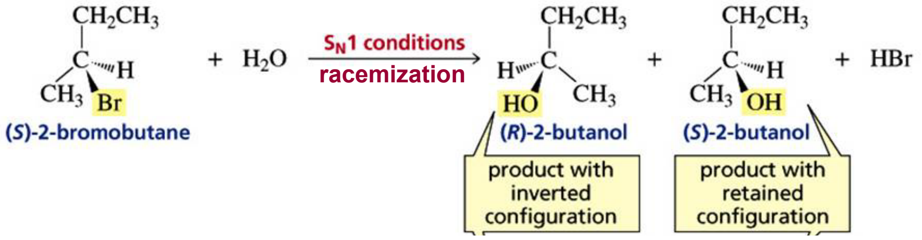


⇨ if substituting at a chiral C: RACEMIC PRODUCT
two stereoisomeric products form in equal quantities

The Stereochemistry of Substitution Reactions

S_N2 → stereospecific (INVERSION)
S_N1 → not stereospecific (RACEMIZATION)





S_N1 reactions don't always lead to <u>complete</u> racemization

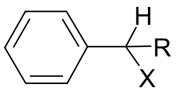
- If leaving group does not move away from vicinity of carbocation before Nu attacks ⇨ one side of C+ is blocked!
- Result: not equal probability of attack from both sides of C+
  ⇨ only <u>partial</u> racemization **(typical: 50-70% inverted product)**

R—X ⟶ **R^+ X^-** ⟶ **R^+ X^-** ⟶ **R^+ X^-**

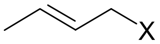
undissociated molecule | **intimate ion pair** | **solvent-separated ion pair** | **dissociated ions**

10.8 Substitutions reactions of benzylic, allylic, vinylic & aryl halides

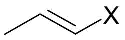
Benzylic:
on C <u>1 bond away</u>
from phenyl ring



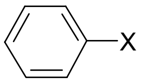
Allylic:
on C <u>1 bond away</u>
from C=C



Vinylic:
on C <u>within</u>
a C=C group



Aryl:
on C <u>within</u>
a phenyl ring



Which can undergo substitution reactions? & which type?

- Consider:
  - a) S_N2: steric hindrance blocking Nu access
    electrostatic repulsion of Nu by p-electrons
  - b) S_N1: stability of carbocation intermediate

Benzylic & allylic halides: CAN do substitution reactions

☑ S_N2 reactions: readily accessible for both benzylic & allylic X's except if tertiary (too sterically hindered)

benzyl chloride

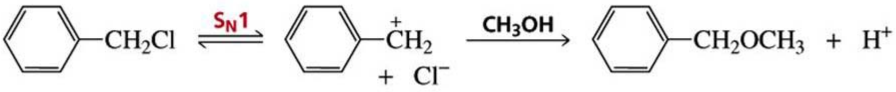
benzyl methyl ether

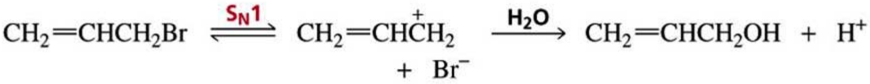
$$CH_3CH{=}CHCH_2Br + HO^- \xrightarrow{S_N2\ \text{conditions}} CH_3CH{=}CHCH_2OH + Br^-$$

1-bromo-2-butene
an allylic halide

2-buten-1-ol

☑ S_N1 reactions: readily accessible for both benzylic & allylic X's
→ carbocation intermediate is resonance-stabilized !

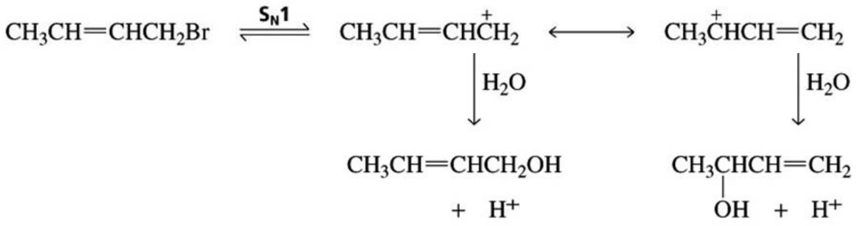




$$CH_2{=}CHCH_2Br \underset{}{\overset{S_N1}{\rightleftharpoons}} CH_2{=}CH\overset{+}{C}H_2 + Br^- \xrightarrow{H_2O} CH_2{=}CHCH_2OH + H^+$$

NOTE: More than 1 product may result from an S_N1 rxn of an allylic halide

→ two C+ carbons evident when draw resonance structures

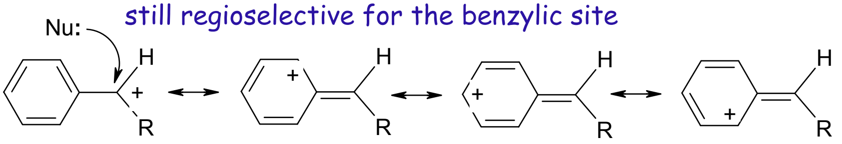


$$\begin{tikzcd} CH_3CH{=}CHCH_2Br \arrow[r, shift left, "S_N1"] & CH_3CH{=}CH\overset{+}{C}H_2 \arrow[l, shift left] \arrow[r, leftrightarrow] \arrow[d, "H_2O"] & CH_3\overset{+}{C}HCH{=}CH_2 \arrow[d, "H_2O"] \\ & CH_3CH{=}CHCH_2OH + H^+ & CH_3\underset{OH}{CH}CH{=}CH_2 + H^+ \end{tikzcd}$$

Multiple products do <u>not</u> occur for benzylic halides

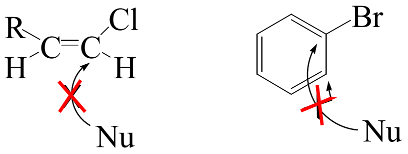
→ attacking within the benzene ring would break ring's "aromaticity" (e⁻s in cyclic array of overlapping p-orbitals gives extra stability)

→ thus: resonance stabilizes the carbocation, but attack by Nu is still regioselective for the benzylic site



Vinyl & aryl halides: CANNOT do substitution reactions

☒ S_N2 reactions: Nu electrostatically repelled by π-electron cloud during approach to back-side of sp^2-carbon

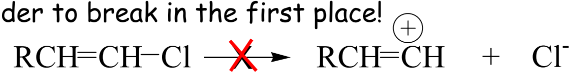


☒ S_N1 reactions: carbocation intermediate is HIGHLY unstable

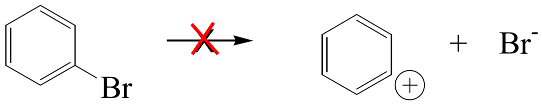
⇨ C+ would rehybridize to become sp-hybridized

⇨ sp-C's have stronger pull on e⁻s ∴ less stable with + charge

Another view: sp^2-C—X bond stronger than sp^3-C—X bonds …so, harder to break in the first place!



$$RCH{=}CH{-}Cl \xrightarrow{\times} RCH{=}\overset{\oplus}{C}H + Cl^-$$



ASSIGNED READINGS

BEFORE NEXT LECTURE:

Read:	Ch.10 up to 10.8
Practice:	predicting products & stereochemistry