Course Chem 343 Lecturer Gellman (11 am)

Day Monday Date 11/07/2011

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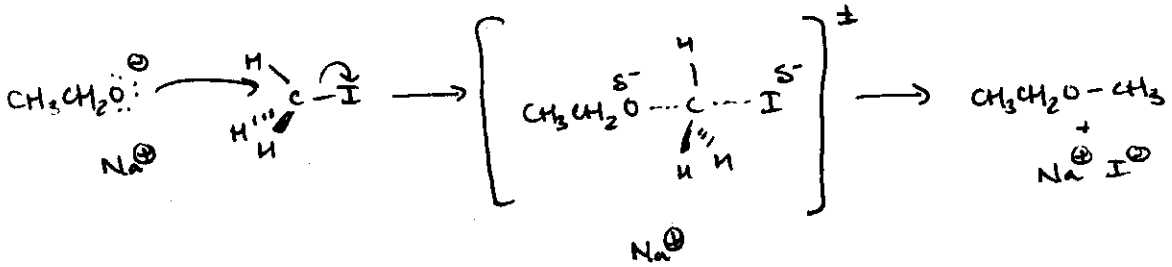
RECALL:

S_N2 ← 2nd Order
↑ ← Nucleophilic
Substitution

Ex:



How can we more accurately understand the mechanism?

Stereochemistry - use of a stereochemically defined substrate - gives insight on direction of nucleophile approach

Ex:

(R)-only (S)-only

* Inversion of configuration at the carbon which undergoes substitution *

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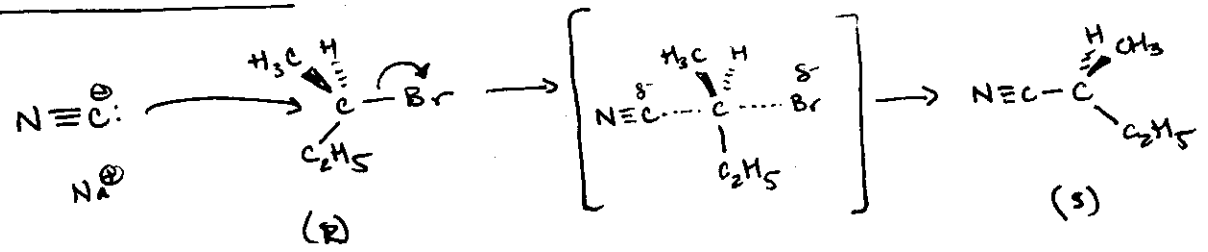
"Backside Attack"



* Why is this directional approach necessary?

→ Molecular Orbital Rationale for "Backside Attack":

C-Br σ* antibonding orbital shown (empty)

Reaction begins with nucleophile lone pair electrons moving into C-Br σ orbital

↳ Necessitates backside attack!

Several Reaction Parameters Influence S_N2 Reactivity

1. Structure of Alkyl Halide (Sterics)
2. Nucleophile Reactivity } Strongly related
3. Solvation
4. Leaving Group.

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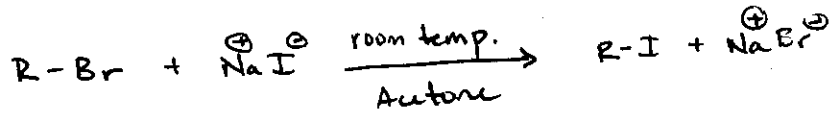
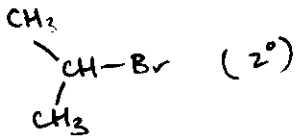
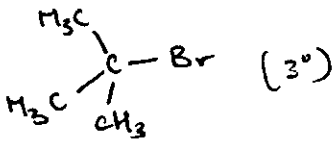
(1) Alkyl Halide Structure

⇒ See Table 9.3 in text.



Alkyl Halide	Relative Rate
CH_3-Br	145
CH_3CH_2-Br (1°)	1.0 ← (point of comparison)
$CH_3CH_2CH_2-Br$ (1°)	0.8
 (2°)	0.008
 (3°)	≈ 0 (essentially no reaction)

(Numbers not important to memorize → KNOW THE TREND!)

KEY TRENDS:

- Methyl > 1° > 2°
- 3° substrates typically don't react by S_N2
- Adding carbons away from the reaction site has little effect on reactivity in most cases → consider:

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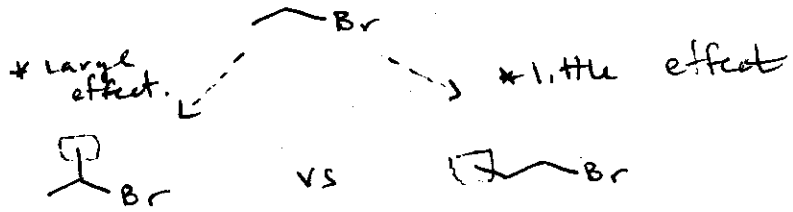
Consider:



* Note: the "neopentyl" effect

Very slow S_N2 (see text)

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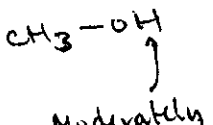
② Nucleophile Reactivity / ③ Solvent Effects

RECALL: Important solvent distinction

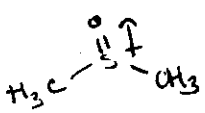
Polar protic solvents vs. Polar aprotic solvents

Ex: Alcohols



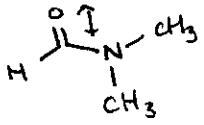
Moderately Acidic

vs.



DMSO

(or)



DMF
(Dimethyl formamide)

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In general: Nucleophiles are more reactive in polar aprotic solvents than in polar protic solvents.

- Also, larger variations in nucleophile reactivity occur in polar protic solvents (relative to polar aprotic) → thus polar aprotic solvents can be more general.

Periodic Trends: (Especially in protic solvents)

↳ Nucleophilic atoms in same column, the lower atom is more Nucleophilic

Ex:

$$\left[R\ddot{O}:^{\ominus} \quad < \quad R\ddot{S}:^{\ominus} \right]$$

less reactive → more reactive

$$\left[I^{\ominus} > Br^{\ominus} > Cl^{\ominus} \right]$$

more reactive → less reactive

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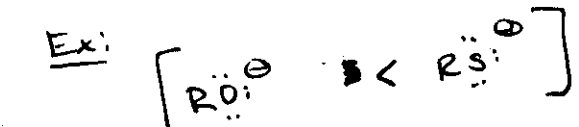
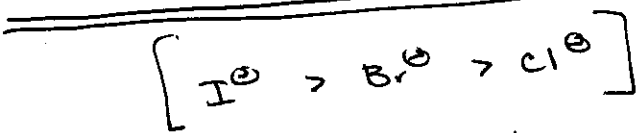


less reactive → more reactive



More reactive → less reactive

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(4) Leaving Group: Effects on S_N2 reactivity

→ Among Halides!

$I^\ominus$ is best Leaving Group (LG)

$F^\ominus$ is terrible LG

($F^\ominus$ is never an S_N2 LG)

Thus:

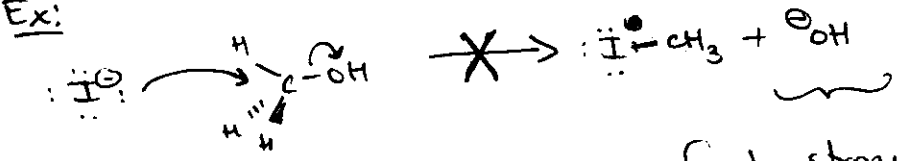
R-I > R-Br > R-Cl (R-F not reactive)

Most reactive ⟶ Least reactive

→ For non-halide Leaving Groups - conjugate bases of strong acids show good Leaving group reactivity, but bases of weak acids are poor Leaving groups.

(conjugate)

Ex:



fairly strong base

⇓

Poor Leaving Group!