(37) **Today**

10.1: Reactivities of Alkyl Halides

11.1 - 11.6: Substitution Reactions

Next Class (38)

Review

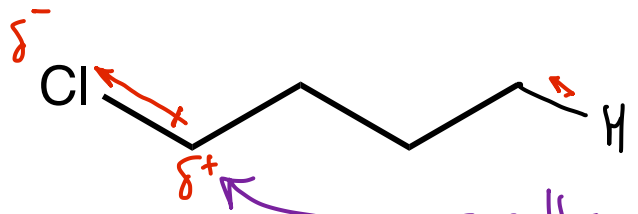
(39) **Second Class from Today**

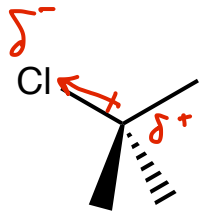
Review

Rework test 3 and hand in on Wednesday, December 10. Remember this is a separate assignment and is worth 5% of your overall grade.

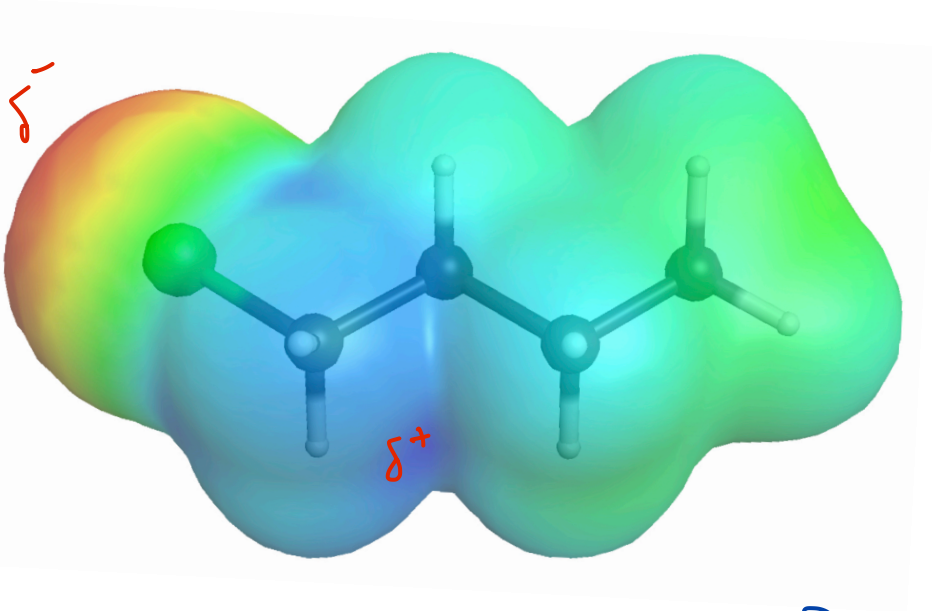
The final for the 9:20 to 10:10 class is Wednesday, December 17 from 12:20 to 2:20.

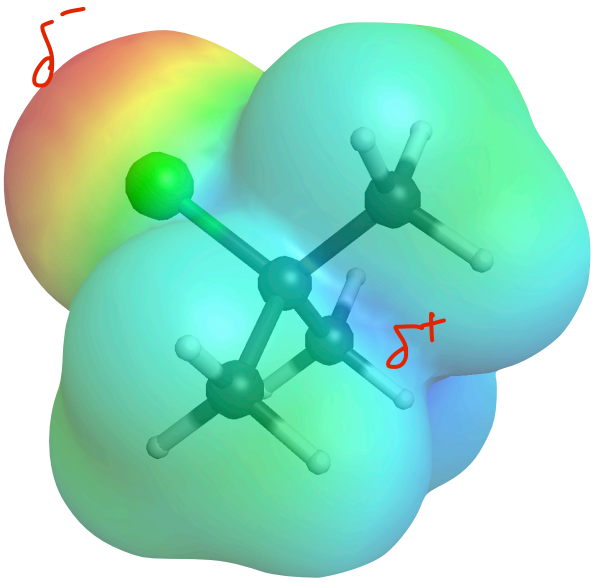
The final for the 10:25 to 11:15 class it is Monday, December 15 from 12:20 to 2:20.





attractive to e⁻ rich things... nucleophiles



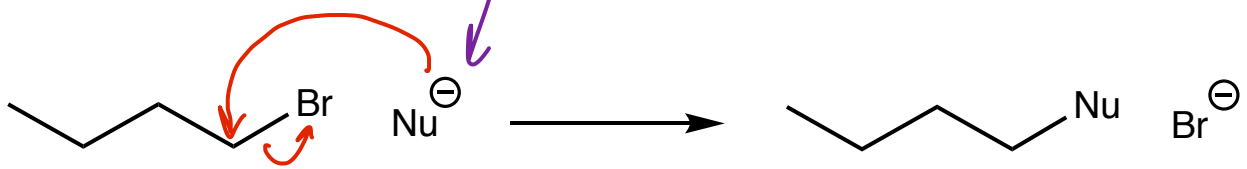


the C atoms at the end of the C to Cl bond are electrophilic

X = Cl^-, Br^-, I^- low energy ions... $NaCl \xrightarrow{H_2O} Na^{\oplus}_{(aq)} + Cl^{\ominus}_{(aq)}$

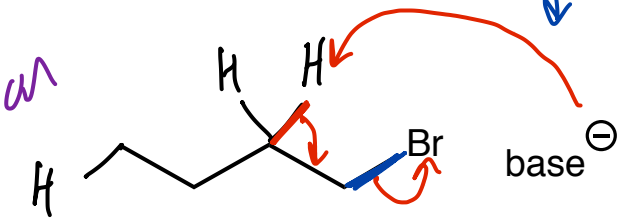
$HX \longrightarrow H^+_{(aq)} + X^-_{(aq)}$ are strong acids because $Cl^{\ominus}$, $Br^{\ominus}$, and $I^{\ominus}$ are low energy ions

Nucleophilic substitution



$^{\ominus}OH$ e^- rich... attractive to electrophiles... nucleophile

$^{\ominus}OH$ e^- rich... high E... can act as a base... abstract H^+

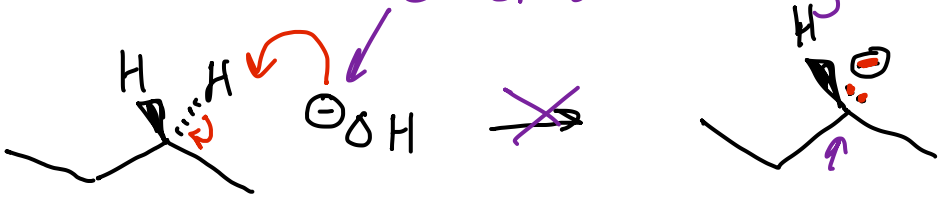


lp e^- from C to Br bond

used to be e^- between the C + H

elimination next semester

$^{\ominus}$ stabilized by $\delta+$ nucleus



Reasonable? No... $C^{\ominus}$ much less stable than $O^{\ominus}$

$^{\ominus}$ stabilized by $\delta+$ nucleus

Overview

Nucleophilic Substitution and Mechanisms of Nucleophilic substitution: predict products and draw mechanisms

SN2 access SN1 C+ stability

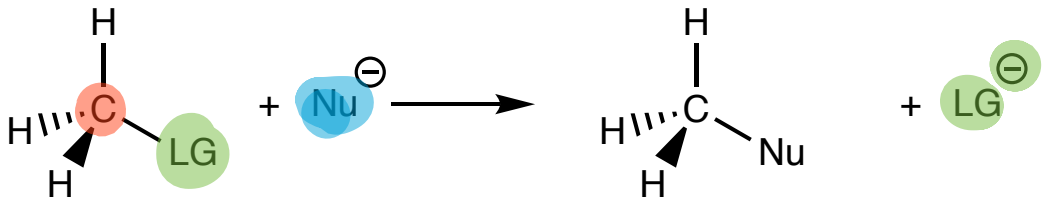
- Factors affecting nucleophilic substitution: describe and explain
- Competition between S_N1 and S_N2 Mechanisms: predict likely predominant mechanism
- Alcohols as Substrates in Substitution Reactions: predict products and describe reactions

Elimination Reactions and Mechanisms of Elimination Reactions

- Factors affecting elimination reactions
- Competition between E1 and E2 Mechanisms
- Alcohols as Substrates in Elimination Reactions

Competition between Substitution and Elimination Reactions

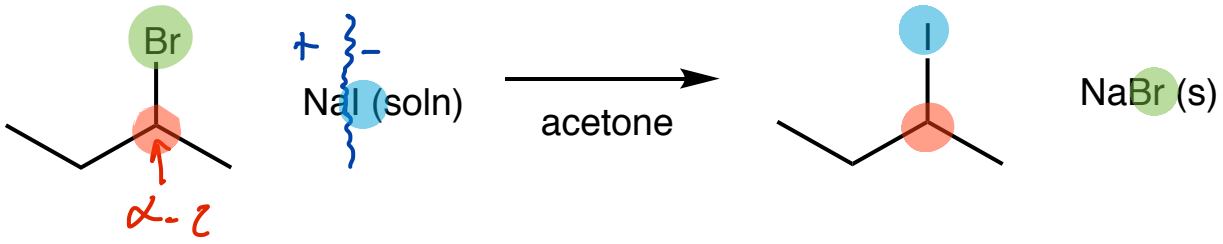
Nu Na



α-Carbon — the C atom with the LG on it / the C atom with the halogen bonded to it / the C atom where the substitution occurs

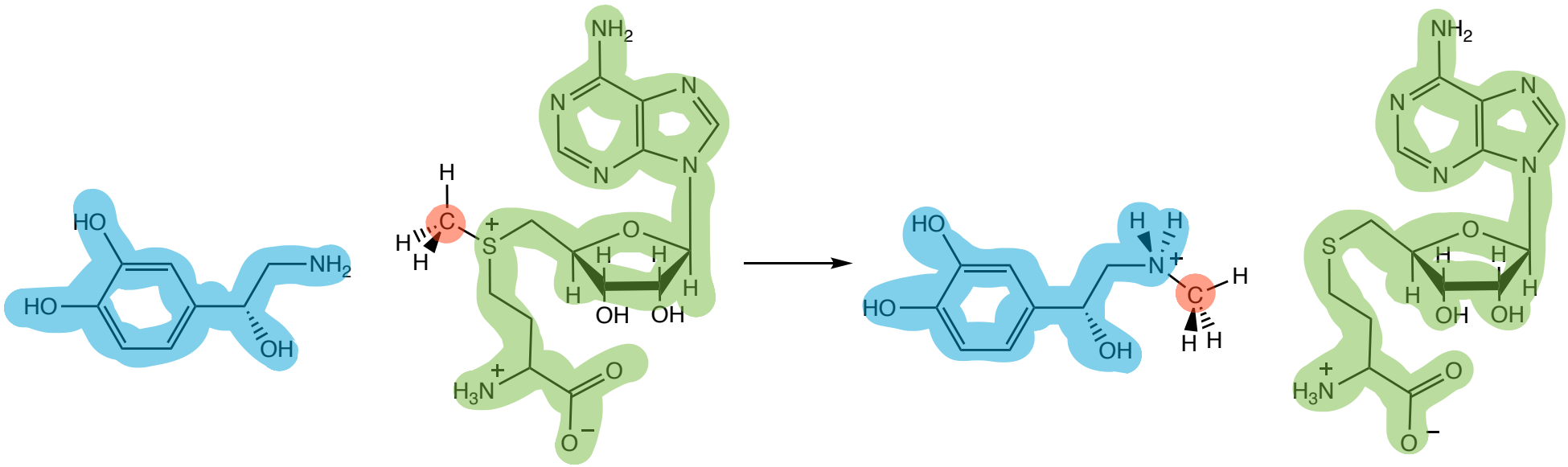
Nucleophile — e⁻ rich atom/ion/molecule that substitutes in for the leaving group

Leaving Group — the atom/group that leaves and carries away e⁻



Nucleophilic Substitution Reactions in Biology

S_N2



norepinephrine
(noradrenaline)

S-adenosylmethionine

epinephrine
(adrenaline)

Nucleophilic Substitution Reactions in Biology

SN1

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The lysozyme mechanism sorted — after 50 years

Anthony J Kirby

Unambiguous evidence for a glycosyl-enzyme intermediate on the lysozyme reaction pathway has recently been reported, finally settling what kind of mechanism this textbook enzyme uses.

The publication in 1965[1] of the hen egg white lysozyme crystal structure — the first such structure of any enzyme — was a major landmark, offering the prospect of detailed explanations of enzyme mechanisms at the molecular level. Such mechanisms involve some of the most subtle relationships between structure and function in all of biology, as enzymes have to recognize and thus stabilize transition states, which probably exist for only femtoseconds. Because the structure of lysozyme was a first, and because of the coherent messages the structure seemed to provide, lysozyme has been a textbook example of enzyme mechanism ever since. Now, in a recent issue of *Nature*, Vocadlo *et al.*[2] report new evidence about the mechanism of lysozyme, information that has been sought after for almost 50 years.

Lysozyme is the most prominent member of the very large class of glycosidases or glycohydrolases, enzymes that catalyze the transfer of a glycosyl group to water. *In vivo* lysozyme catalyzes the hydrolysis of a polysaccharide component of the cell wall of Gram-positive bacteria. To do this it accelerates enormously the extraordi-

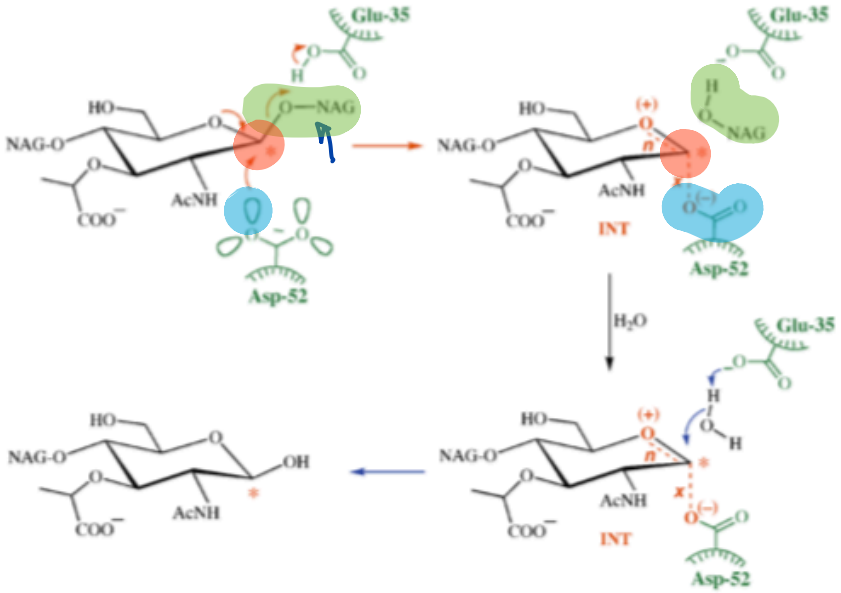
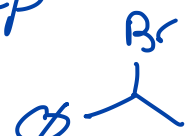


Fig. 1 The reaction catalyzed by lysozyme. The substrate is bound so that the leaving group oxygen, the 4-OH group of an N-acetylglucosamine (NAG) residue, is protonated as it leaves by the COOH group of Glu 35. Groups on the enzyme are colored green, electron movements and the key developing bonds and charges in red. Only one of the dashed *exo* and *endo* (*x* and *n*) bonds of the intermediate (INT) is actually present: which one defines the mechanism. Thus *n* is missing in mechanism (i), *x* in mechanism (ii).

Nature structural biology (2001), v8(9), p73

S_N2 is because two things collide in the rate determining (only) step

I^- +  collide

2 = bimolecular

LG leaves and a C^+ Forms.

In this example a 3° C^+ is next to π bonds + is stabilized by e^- delocalization

Nucleophile has to wait for one molecule to ionize

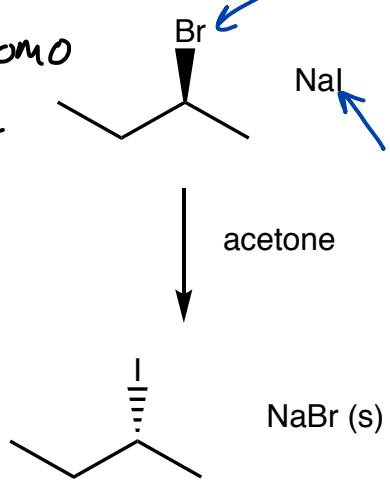
S_N1

Which mechanism runs depends on reactants and conditions used

Evidence for S_N2 and S_N1

Section 11.2 and 11.4

(S)-2-bromo butane



Br is blocking the front

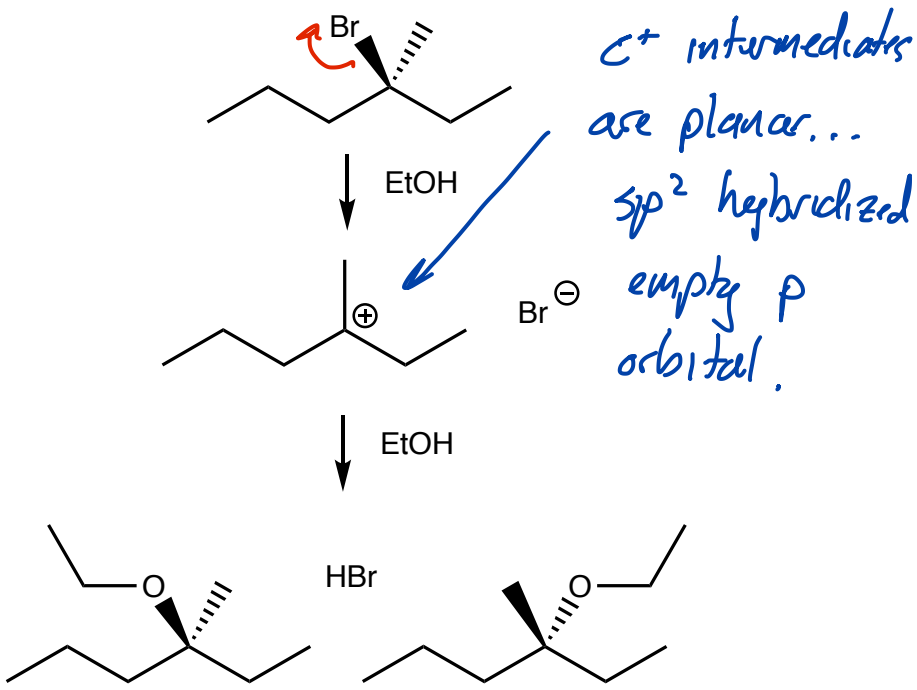
I^- cannot come in from the front. The I^- must come in from behind

S_N2 occurs via backside attack of the α-C

enantiomerically pure reactant

↓

inverted and enantiomerically pure product



C^+ intermediate are planar... sp^2 hybridized empty p orbital.

S_N1 forms C^+ so the Nu can come in from either side

enantiomerically pure reactant

↓

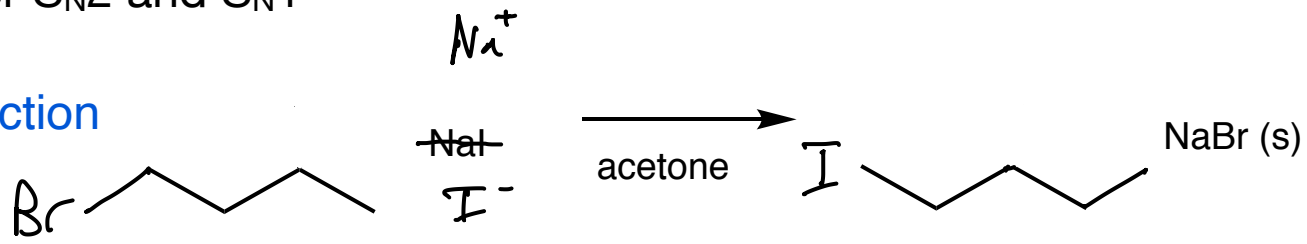
mixture of enantiomers in the product

Rate laws must be determined experimentally: rate = k [A]^x[B]^y

Evidence for S_N2 and S_N1

Section 11.2 and 11.4

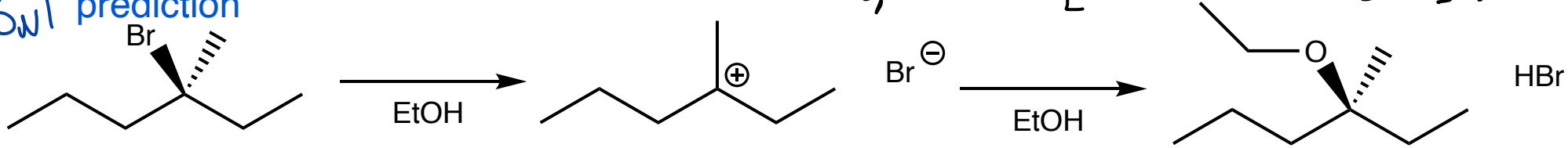
S_N2 prediction



rate = k [$CH_3CH_2CH_2CH_2Br$][I^-]^1

Since each molecule must collide with the other, doubling the conc of one doubles the chance of a collision ... so you would be doubling the rate. Thus, S_N2 predicts that rate is 1st order with respect to [substrate] & [Nu].

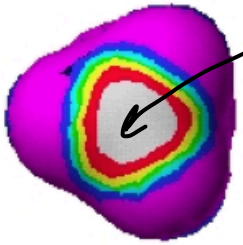
S_N1 prediction



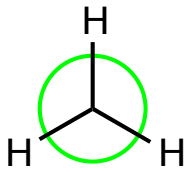
rate = k [$CH_3CH_2CH_2C(CH_3)BrCH_3$][Nu]^0

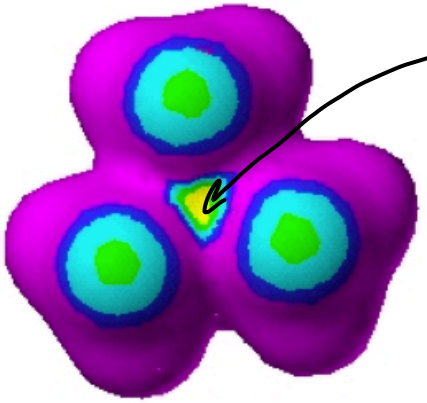
Since Nu is not present in the rate determining step, the rxn is zero order w/r/t [Nu]

Rate does not depend on the conc of the Nu.

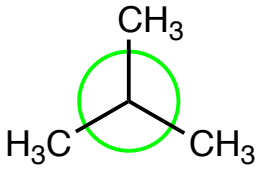


huge bull's eye





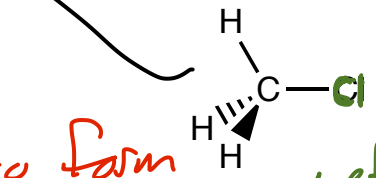
bull's eye is gone



bull's-eye shows where molecule is likely to do nucleophilic substitution

great S_N2 site

methyl

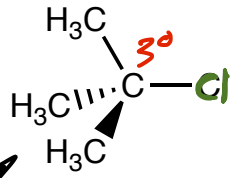


S_N2

methyl, 1°, 2°

c+ not going to form

3° c+ much more stable



S_N1

not a good substrate for S_N2