(17) **Today**

Sections 11.1 - 11.6: Substitution Reactions

Next Class (18)

Sections 11.1 - 11.6: Substitution Reactions

Sections 10.5, 17.6: Alcohols in Nucleophilic Substitution Reactions

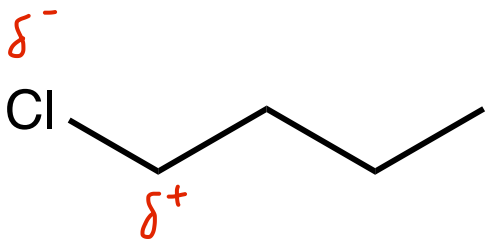
(19) **Second Class from Today**

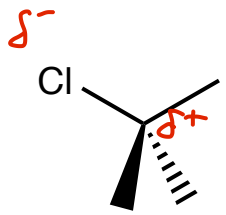
Sections 11.1 - 11.6: Substitution Reactions

Sections 10.5, 17.6: Alcohols in Nucleophilic Substitution Reactions

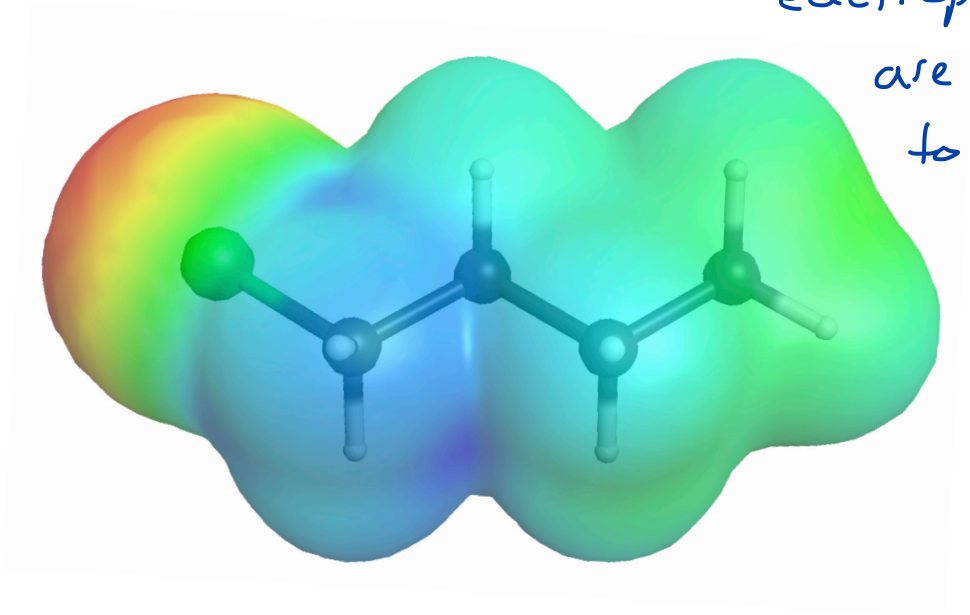
Third Class from Today

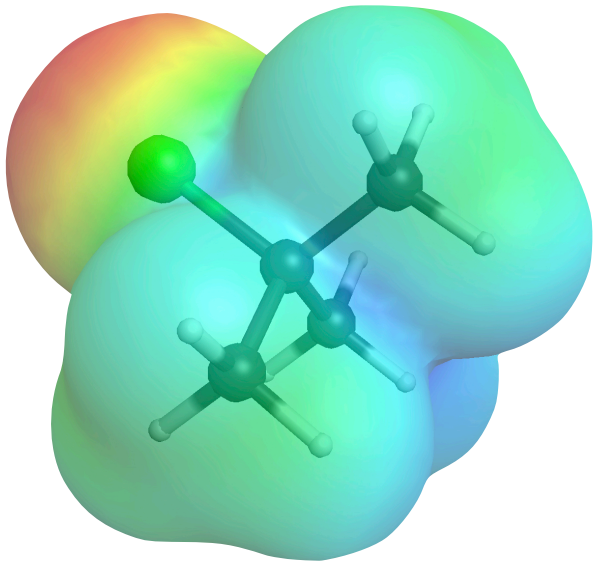
Last Exam





these C atoms are electrophiles ... they are attractive to nucleophiles

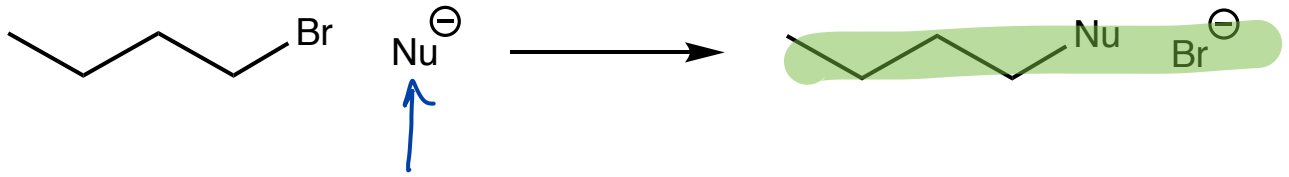




Substitution and Elimination are Possible

Sections 11.1 and 11.7

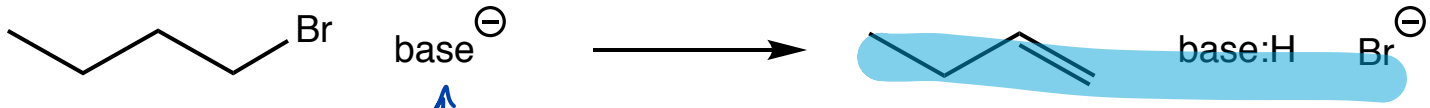
11.1 – 11.6



a generic e⁻ rich atom or molecule

Nu substituted in for Br

11.7 – 11...



a generic base

Both nucleophiles and bases are electron rich and that means that a nucleophile could act as a base….
Depending on the specific conditions, elimination and substitution are possible.

Overview

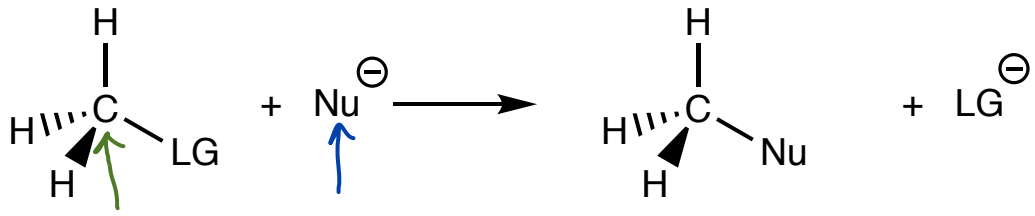
Nucleophilic Substitution and Mechanisms of Nucleophilic substitution: predict products and draw mechanisms

- 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 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

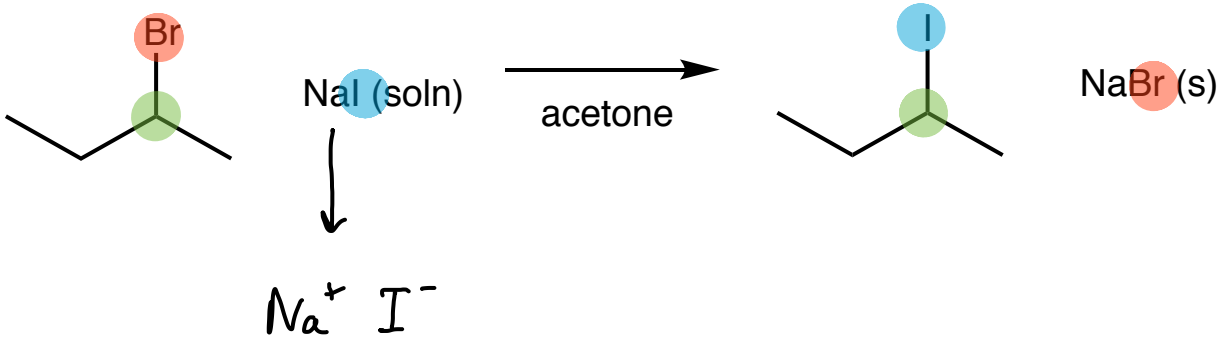
Competition between Substitution and Elimination Reactions



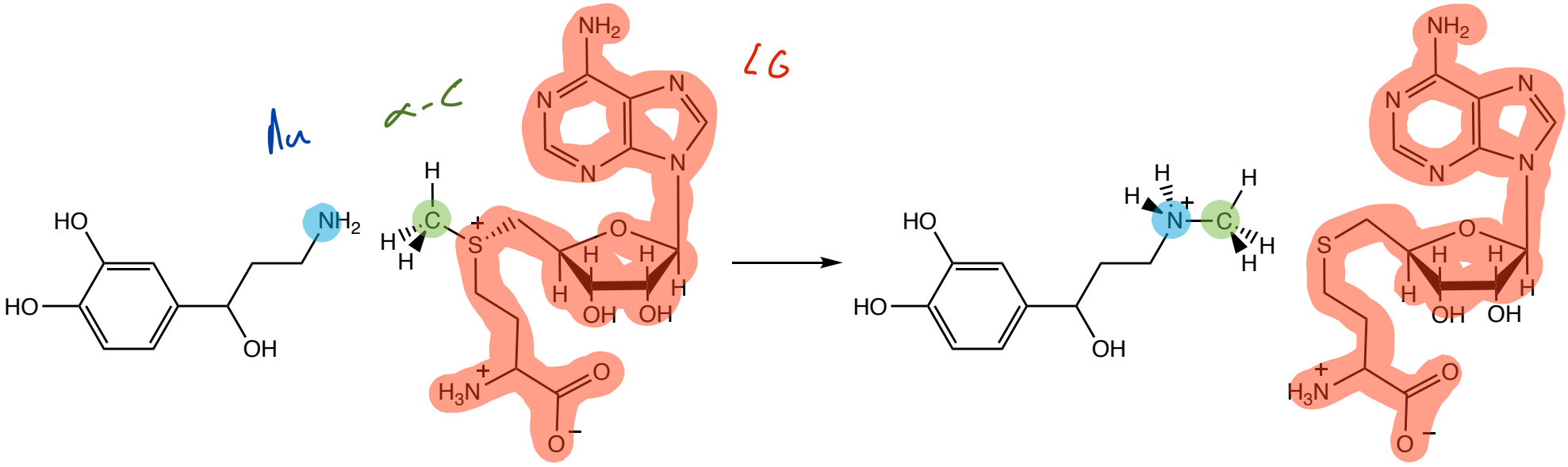
α-Carbon the C atom where the substitution occurs

Nucleophile the e⁻ rich molecule or atom that forms a new bond to the α-carbon

Leaving Group the atom or group of atoms that leaves carrying away 2 e⁻'s to make room for the Nu to form the new bond to C



Nucleophilic Substitution Reactions in Biology



Nucleophilic Substitution Reactions in Biology

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-

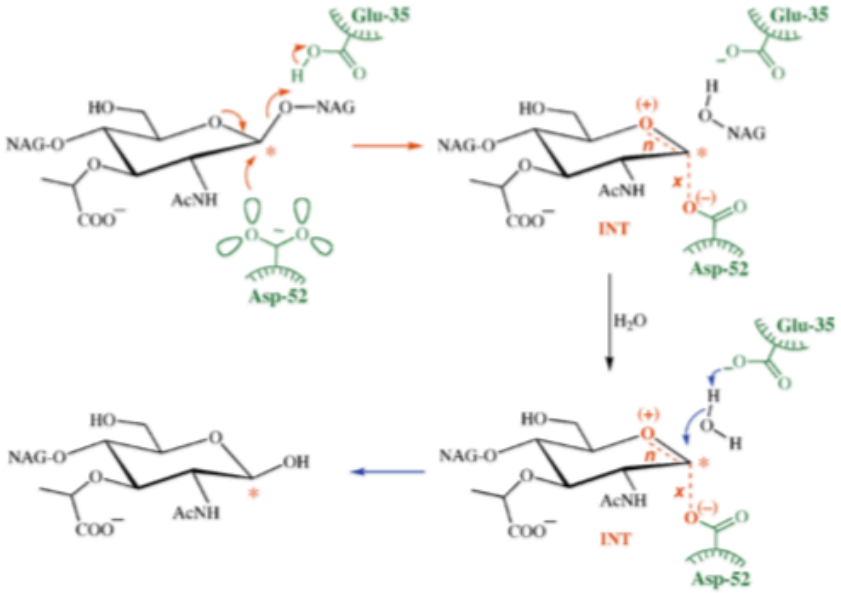
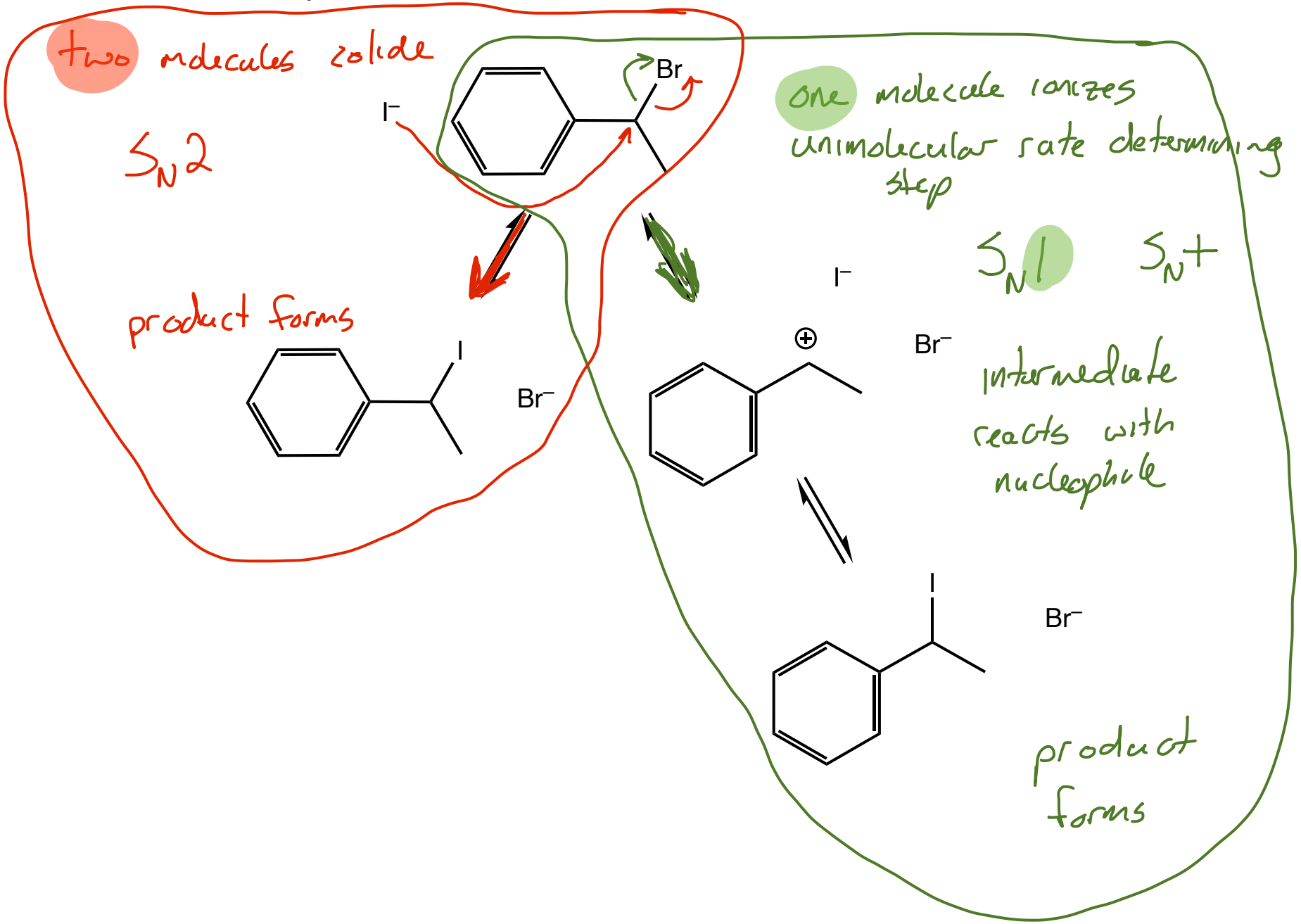
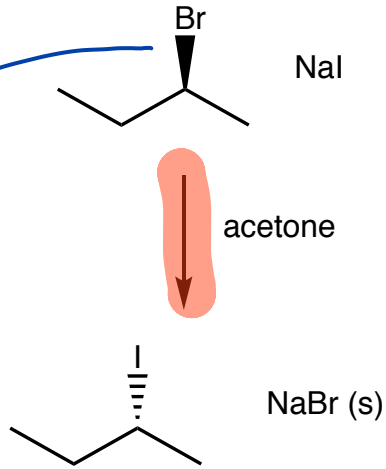


Fig. 1 The reaction catalyzed by lysozyme. The substrate is bound so that the leaving group oxygen, the 4-OH group of an N-acetylglucosamine (NAG) residue, is protonated as it leaves by the COOH group of Glu 35. Groups on the enzyme are colored green, electron movements and the key developing bonds and 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).

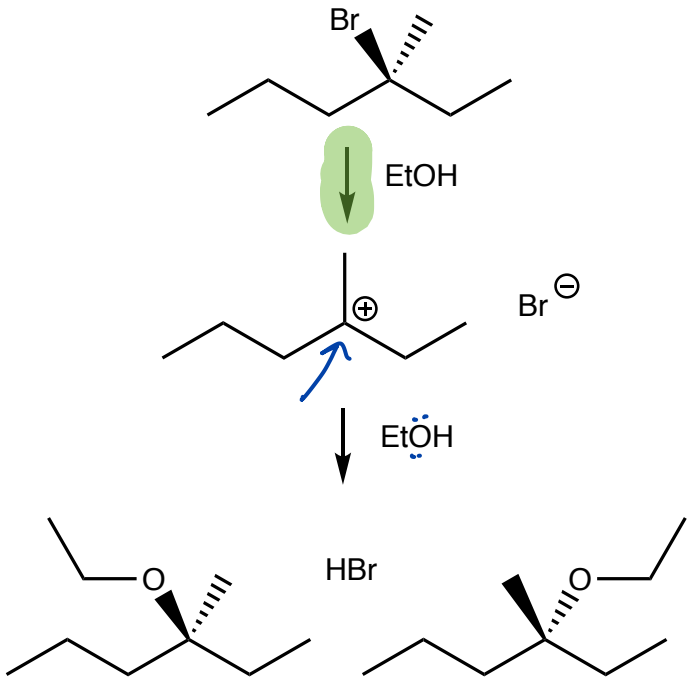
Nature structural biology (2001), v8(9), p73


two molecules collide
S_N2
I⁻
Br
product forms
I
Br⁻
one molecule ionizes
unimolecular rate determining step
S_N1
S_N+
I⁻
⊕
Br⁻
intermediate reacts with nucleophile
I
Br⁻
product forms

Evidence for S_N2 and S_N1

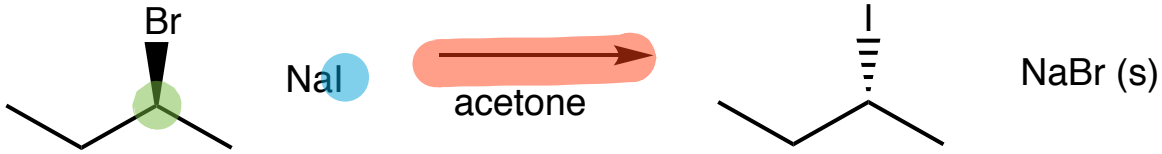


- The Br is blocking the front face
- The e⁻ rich I^- would be repelled by the e⁻ rich Br if it tries to bond to the front face
- The Nu (I^-) must come in from behind — back side attack
  - S_N2 rxns occur with inversion of stereochemistry of α-C



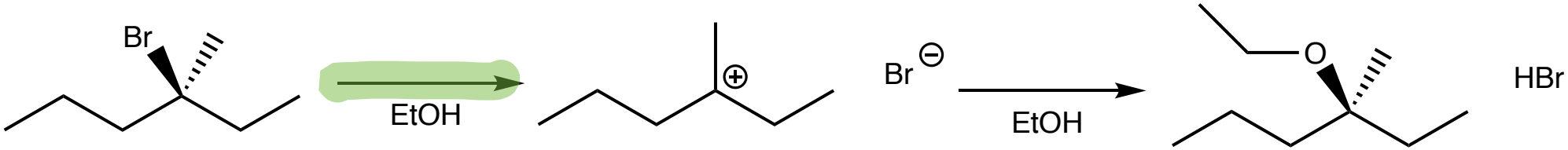
- Since a C^+ forms the nucleophile can add to the front or back face
- Both stereoisomers are formed

Evidence for S_N2 and S_N1



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

rate depends on the concentration of both molecules

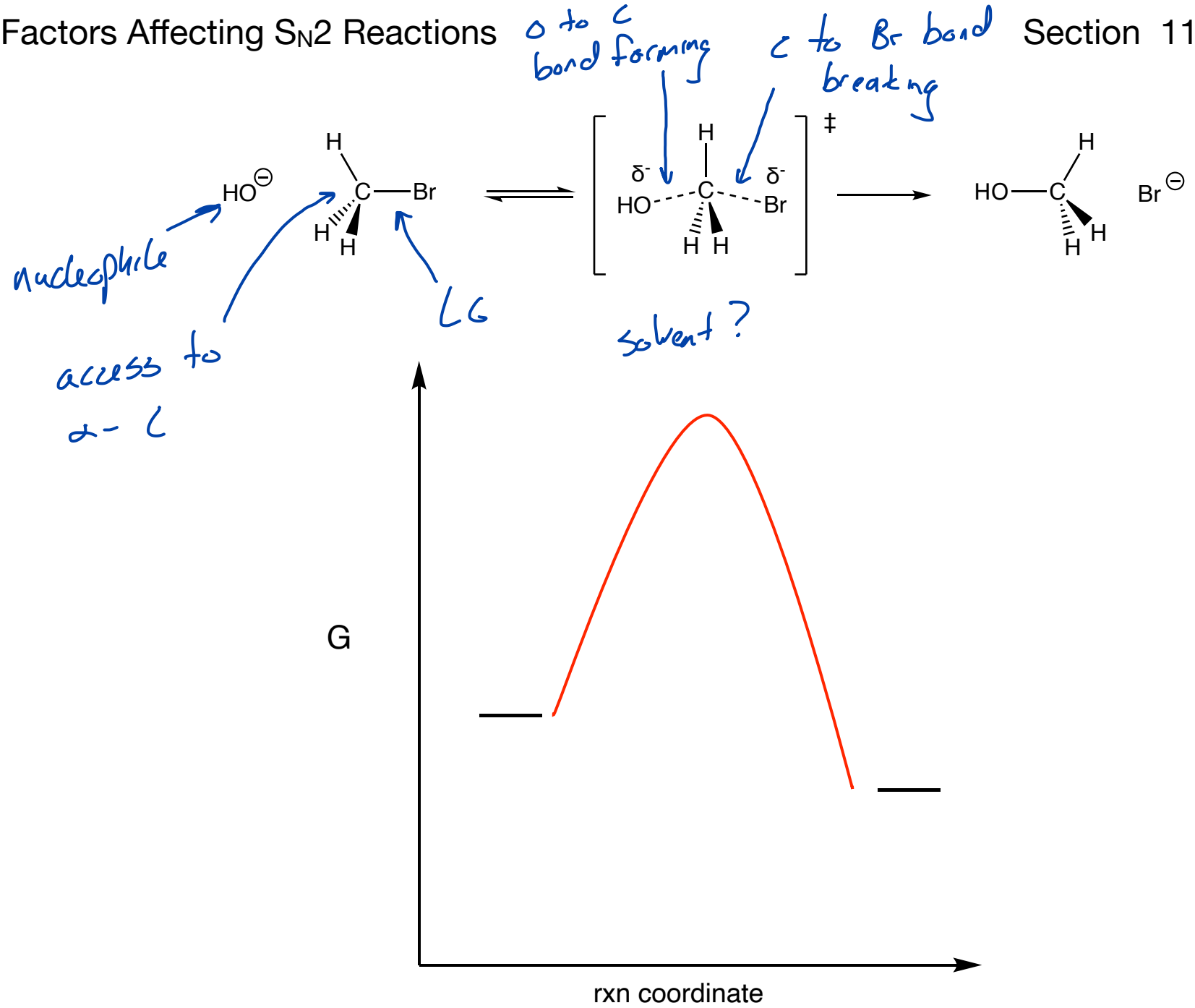


rate = k [$CH_3CH_2CH_2C(CH_3)BrCH_3$]

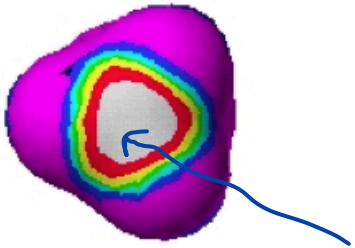
rate depends on ionization of α-C then changing the conc of the nucleophile doesn't change rate

Factors Affecting S_N2 Reactions

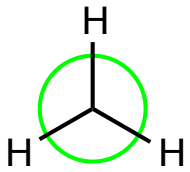
Section 11.2 and 11.3



Newman Projection

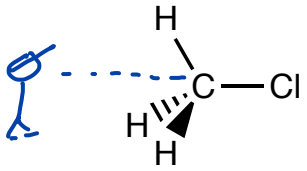


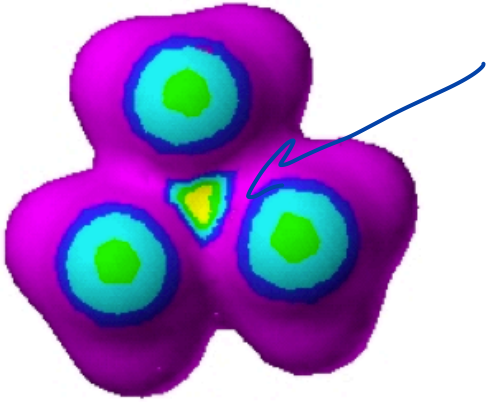
bullseye



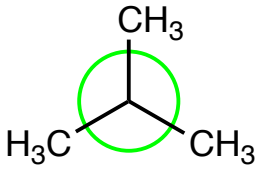
methyl α-C

great access to backside of α-C



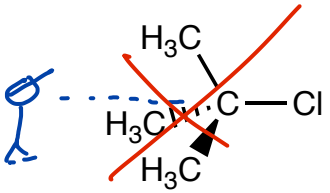


no bullseye



3° α-C

methyl groups are blocking access to the back side of the α-C



too crowded to do S_N2

Nucleophilic frontier density... shows where a nucleophile is likely to attack