CHEM202

Stereochemistry

Lecture 7

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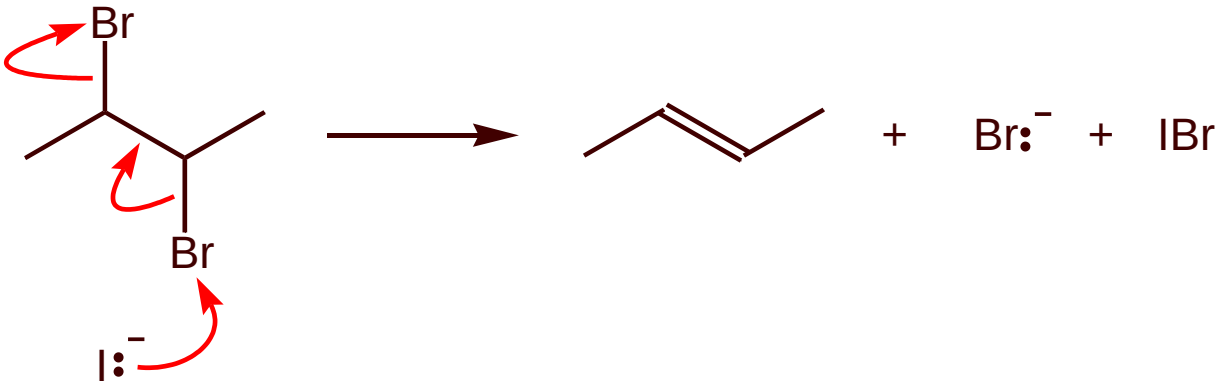
Cover

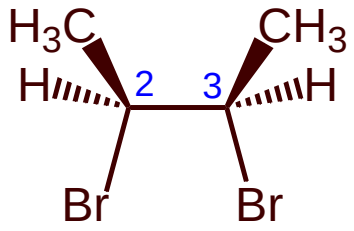
Ease of Access

Synthesis Design

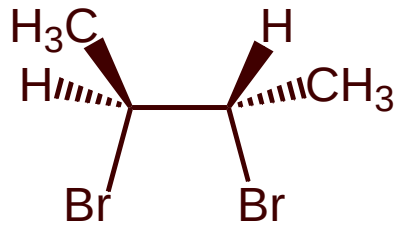
A dibromide may be converted into an alkene with $I:^-$ in an E2 reaction:



Which dibromide (**A** or **B**) would you use to make (*Z*)-2-butene?



*achiral form (**A**)*



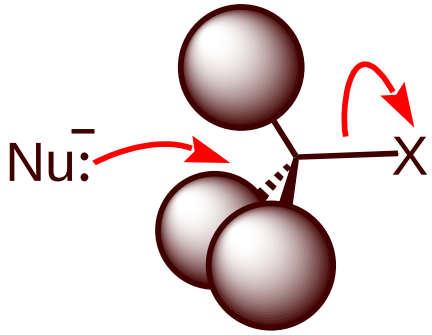
*chiral form (**B**)*

Steps:

- Draw a Newman projection along the 2,3-bond.
- Draw a Newman projection with anti-periplanar Br, C-2, C-3, Br.
- Deduce the relative orientations of the CH_3 groups.

Ease of Access

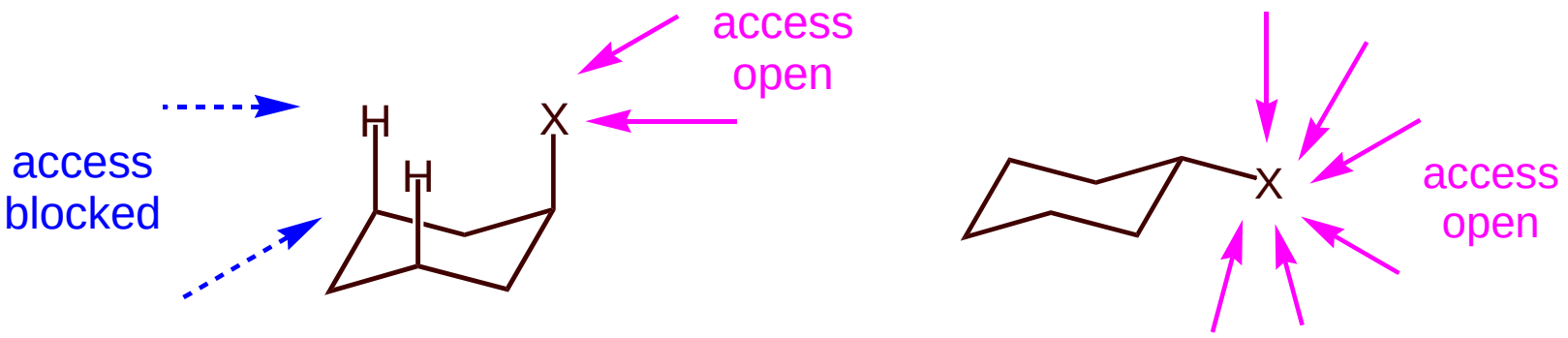
In S_N2 (CHEM 191), ease of access to the back side of the reactant is a key factor:



- Large groups attached to the carbon under attack slow the reaction
- Similar control is common in other reactions
- This is particularly so in reactions of cyclohexane derivatives

Ease of Access in Cyclohexane Derivatives

- Shows up in the relative reactivity of pairs of epimers
- The key to recognising this control:
  - The reagent attacks at a centre outside ring - *exocyclic attack*
- Controlling influence - different environments of axial and equatorial groups:
  - Axial attack is partially blocked by other axial groups on same side of the ring, *i.e.* groups in a 1,3-*cis* relationship
  - Equatorial groups are much more accessible



Esterification of Alcohols

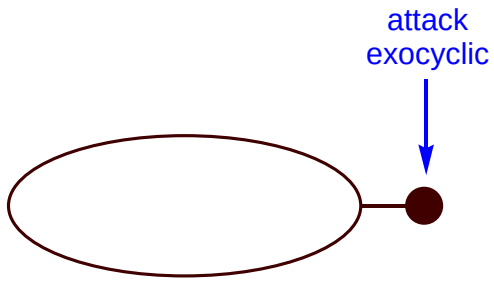
Alcohol + acid halide $\Rightarrow$ ester (acetate as shown) (CHEM 191):

$$ROH + CH_3COCl \rightarrow ROCOCH_3 + HCl$$

Mechanism

For a cyclohexanol:

- The R group contains the cyclohexane ring
- In the rate controlling step, the acid chloride must collide with the oxygen of the alcohol
- Attack is at an exocyclic centre (outside the ring)
- Ease of access is important
- An equatorial alcohol esterifies faster than its axial epimer



Hydrolysis of Esters

The reverse reaction, ester hydrolysis, is under similar control (CHEM 191):

Mechanism

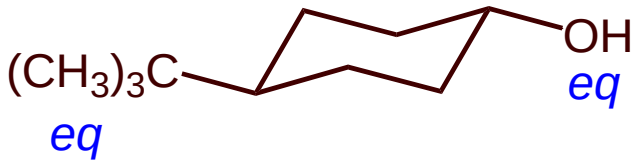
The key attack is at an exocyclic centre

- Equatorial esters react faster than axial
- Thus, if an alcohol esterifies rapidly, its ester will also hydrolyse rapidly

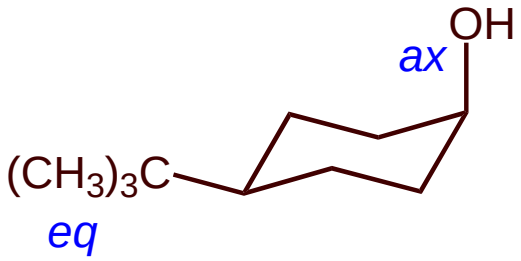
Simple Cyclohexanols

Compare esterification of *cis* and *trans*-4-*tert* butylcyclohexanol:

- The bulky *tert*-butyl group must be equatorial
- The form with an axial *tert*-butyl group is destabilised by 1,3-diaxial interactions
- Thus, there is only one chair form for each reactant
- *Trans*-isomer:
  - Has a less hindered equatorial OH
  - Will esterify quickly



- *Cis*-isomer:
  - Has a more hindered axial OH
  - Will esterify slowly



- Analysis of systems that can interconvert chairs is complicated

Steroidal Reactions

- The same concepts apply to analysis of exocyclic reactions in steroids
- A simplification - steroids do not show chair-chair interconversion
- Thus, one can state unequivocally whether a particular substituent is axial or equatorial

Examples of Steroidal Reactions

Conformational analysis can:

- Predict relative rates of reaction for a pair of epimers:

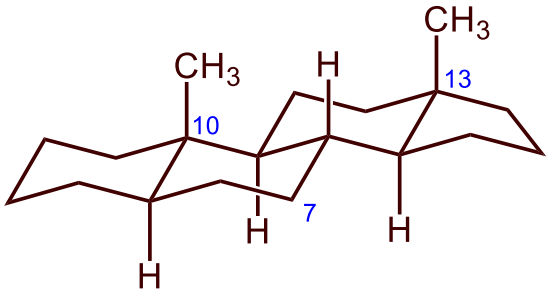
  e.g androstan-2-ol epimers

- Predict relative ease of reaction for different positions in steroid nucleus

  e.g. androstan-3α-ol and androstan-11β-ol

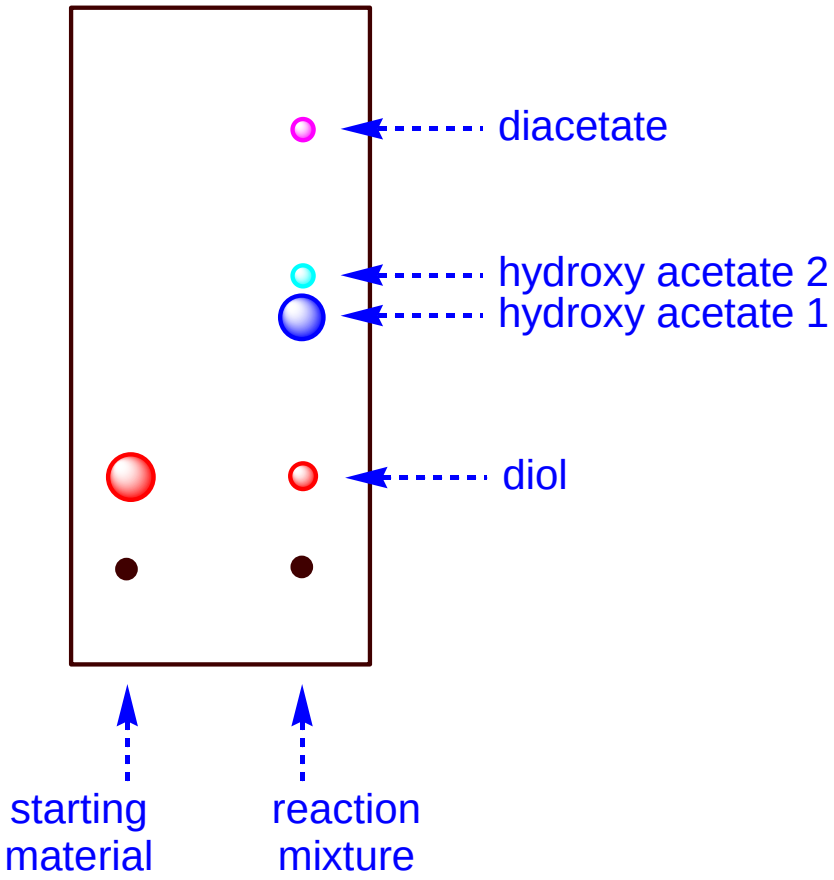
  Help to assess the likely success of a selective functionalization of a polyfunctional molecule

  e.g. androstane-3β,11β-diol



How to Selectively Acetylate a Diol

- Operate at the lowest possible temperature to:
  - maximize selectivity
  - avoid unwanted side-reactions
- Follow the progress of the reaction carefully, *e.g.* by thin-layer chromatography (TLC)



Lecture Problem

How would you make 11β-acetoxyandrostan-3β-ol from androstane-3β,11β-diol?