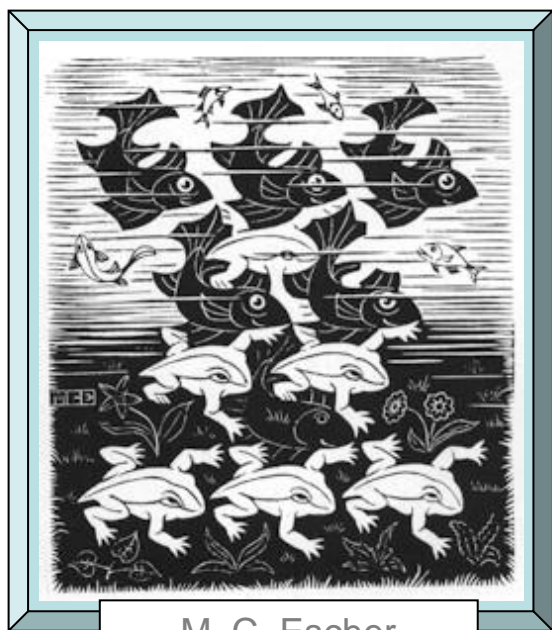


# CHEM202

## Stereochemistry

### Lecture 8

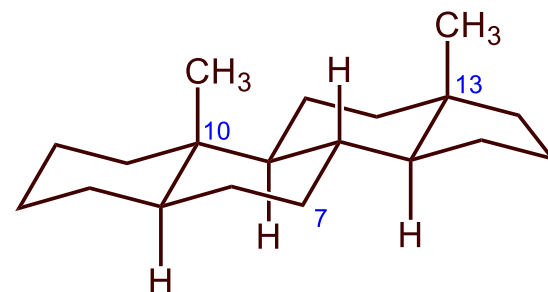
#### Steric Acceleration



M. C. Escher  
Fish & Frogs

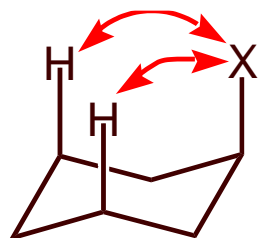
## Lecture Problem

How would you make  $11\beta$ -acetoxyandrostane- $3\beta$ -ol from androstane- $3\beta,11\beta$ -diol?

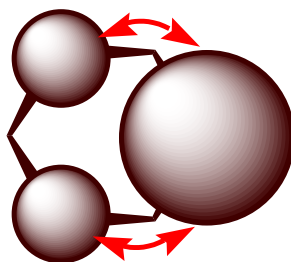


# Steric Compression

Look at this in the setting of the cyclohexane ring. Axial substituents suffer destabilising 1,3-diaxial interactions:



side view

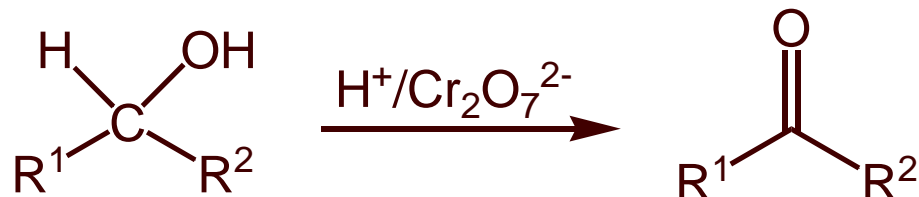


top view

- In reaction where an axial bond is broken:
  - Relief of steric strain may be considerable. May lead to a rate enhancement
  - *i.e.* an axial derivative may react faster than its equatorial epimer
- Characteristic feature:
  - Reaction takes place at ring atom rather than at group attached to ring - *Endocyclic attack*

## Oxidation of Secondary Alcohols

Chromic acid ( $\text{H}^+/\text{Cr}_2\text{O}_7^{2-}$ ) converts 2° alcohols into ketones:



Evidence for slow step:

- Isotope labelling studies:
  - Based on the fact that a C-<sup>2</sup>H bond is stronger than a C-<sup>1</sup>H bond
  - Compare oxidation rates for cholestan-3 $\alpha$ -ol and 3 $\beta$ -deuterocholestan-3 $\alpha$ -ol - get a ratio of 7:1
  - Only expect a large rate difference if the C-H bond is broken in the slow step of the reaction (rate determining step)
- Reaction rate increases if a stronger base is used

## Axial Reacts Faster than Equatorial

Note that the rate controlling step involves:

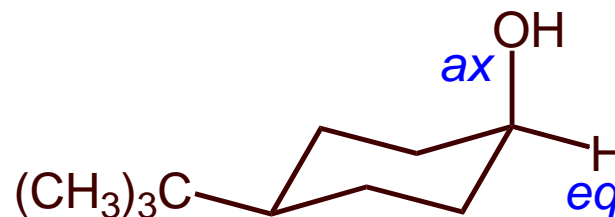
- Conversion of a tetrahedral ( $sp^3$ ) carbon into a planar ( $sp^2$ ) geometry – attack at an endocyclic centre
  - For an axial ROH get relief of strain from 1,3-diaxial interactions
  - For most equatorial ROH get little steric relief
- Removal of a proton by a base ( $H_2O$ ) – exocyclic attack
  - This is easier for an equatorial hydrogen

Thus, for an axial alcohol the two factors combine. An axial alcohol oxidises faster than its equatorial epimer

## Simple Cyclohexanols

4-*tert*-butylcyclohexanols:

- *Cis*-isomer:
  - Has an axial OH
  - Reaction removes 1,3-diaxial interactions
  - H<sub>2</sub>O has easy approach towards the equatorial hydrogen



## Simple Cyclohexanols

4-*tert*-butylcyclohexanols:

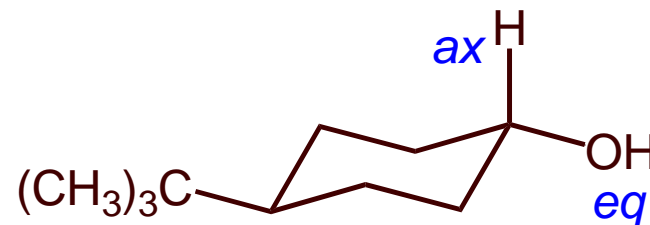
- *Cis*-isomer:

- Has an axial OH
- Reaction removes 1,3-diaxial interactions
- H<sub>2</sub>O has easy approach towards the equatorial hydrogen



- *Trans*-isomer:

- Has an equatorial OH
- Reaction provides little steric relief
- Approach of H<sub>2</sub>O to the axial hydrogen is more difficult



- Thus, the *cis*-isomer reacts more rapidly than the *trans*

# Steroidal Alcohols

Relative rate data for oxidation of a range of cholestanols:

## Axial

## Equatorial

1 $\alpha$ -ol 13.0

1 $\beta$ -ol 9.7

2 $\beta$ -ol 20.0

2 $\alpha$ -ol 1.3

3 $\alpha$ -ol 3.0

3 $\beta$ -ol 1.0

4 $\beta$ -ol 35.0

4 $\alpha$ -ol 2.0

6 $\beta$ -ol 36.0

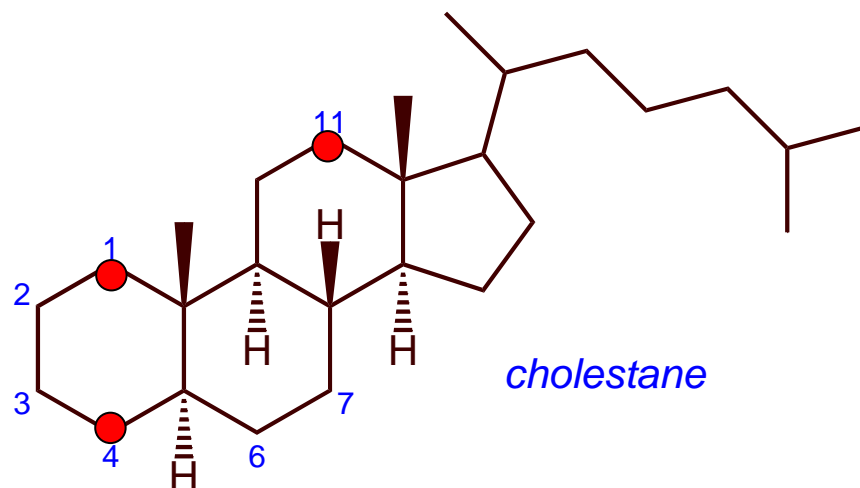
6 $\alpha$ -ol 2.0

7 $\alpha$ -ol 12.3

7 $\beta$ -ol 3.3

11 $\beta$ -ol 900.0

11 $\alpha$ -ol 14.0



Note:

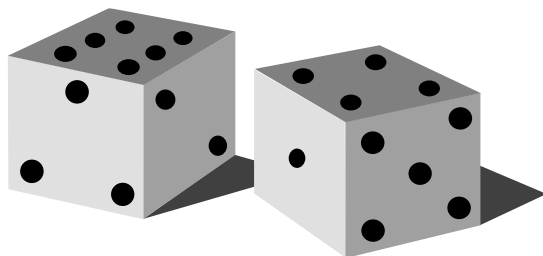
- An axial ROH always reacts faster than its equatorial epimer
- The most reactive axial ROH are the most sterically hindered
- A hindered equatorial ROH will also react rapidly



## Selective Syntheses

- Use combinations of oxidation, acetylation and hydrolysis
- Use principles discussed over the last 2 lectures
- Design selective syntheses of multifunctional steroids
  - A game of logic

## Game Rules (Limited sub-set)



## Selectivity

- *Axial Groups*
  - oxidation fast
  - hydrolysis and esterification slow
- *Equatorial Groups*
  - oxidation slow
  - hydrolysis and esterification fast

## Protection

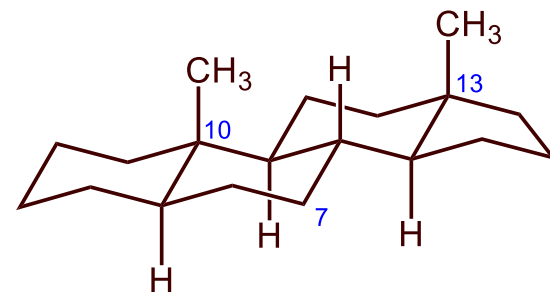
- OAc group is not oxidised

## Lecture Problem

Design syntheses of:

- $2\alpha$ -hydroxyandrostan-6-one
- $6\beta$ -hydroxyandrostan-2-one

starting from androstane- $2\alpha$ ,  $6\beta$ -diol



## Recap/Tute

Represent as regular polygons

Each unspecified vertex is a C with enough H to give 4 bonds

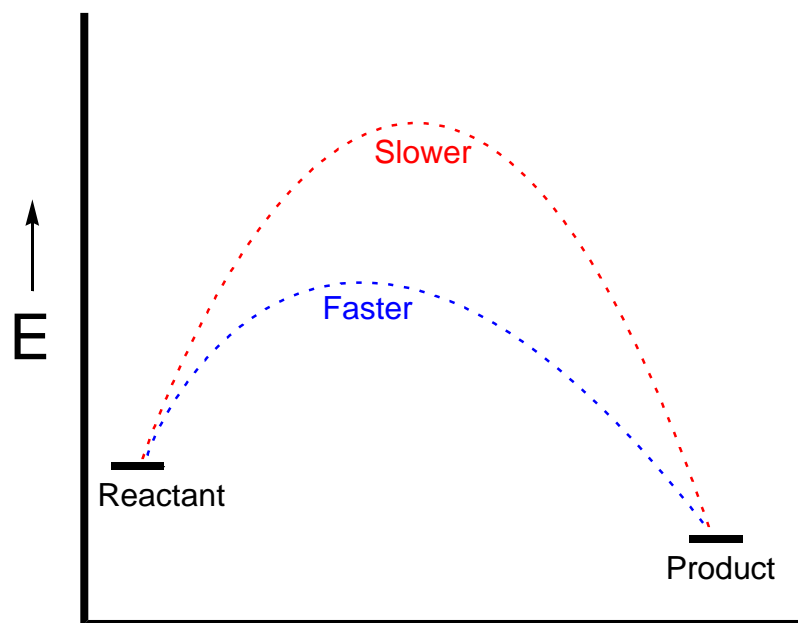
Name by adding *cyclo* to alkane name

Molecular shapes dictated by minimisation of:

- *Bond Angle Strain* - bond angles will be as close as possible to the ideal
- *Torsional Strain* - adjacent bonds will be as close to staggered as possible
- *Van der Waals Interactions* - close approach of non-bonded atoms will be avoided if possible

## Irreversible Ring Formation

- Irreversible ring formations are controlled by the rate of product formation (*kinetic control*)
- The lower the activation energy, the faster the product will form

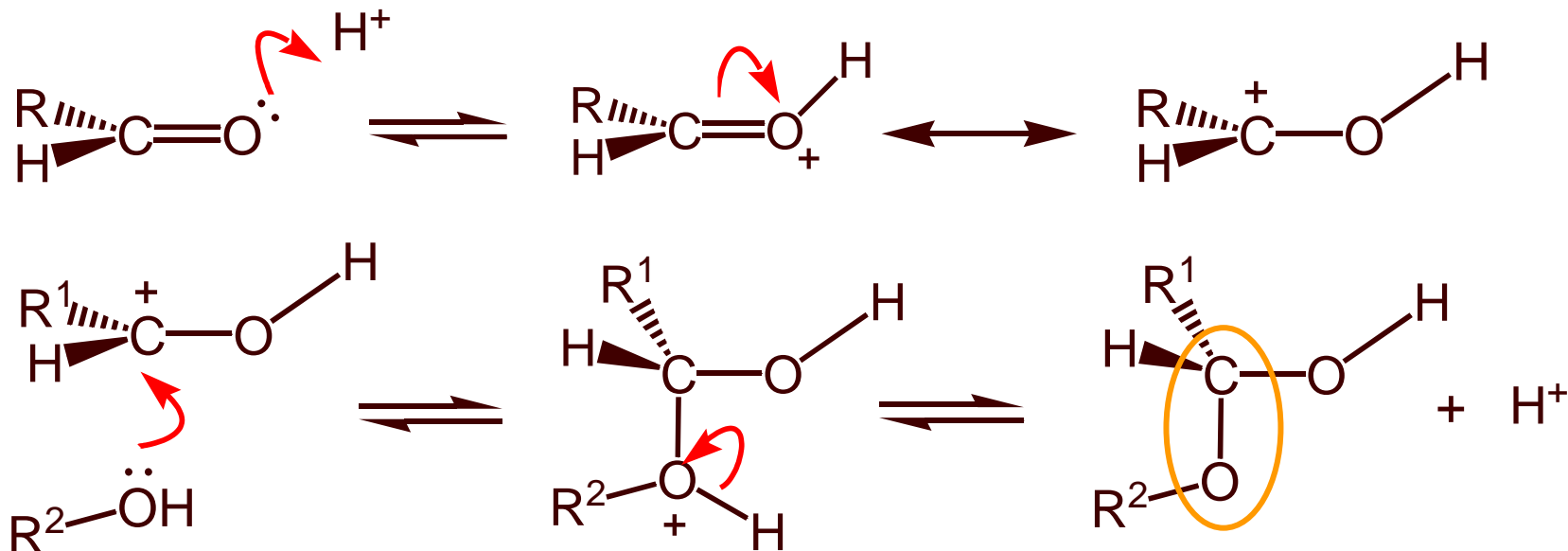


## Reversible Ring Formation

- These reactions are under *thermodynamic control*
- Equilibrium composition reflects the stability of the ring system
- Cyclized products may only be isolated if the ring has little strain

# Hemiacetal Formation

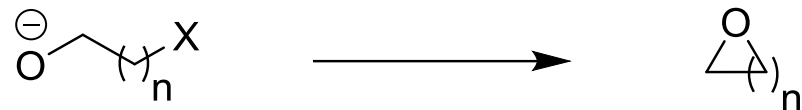
- Results when an alcohol and an aldehyde are treated with acid (CHEM 191)



# Cyclic Ethers

- Alkoxide + alkyl halide  $\Rightarrow$  ether ( $S_N2$  reaction – CHEM 191)
- If both functions are part of the same molecule  $\Rightarrow$  cyclic ether
- Not reversible - halide ion (nucleophile) cannot displace alkoxide ion (poor leaving group)
- Rate of reaction strongly dependent on ring size. Observations:

–  $3 \approx 5 > 6 > 4 \approx 7 > 8$



– 8-membered ring:

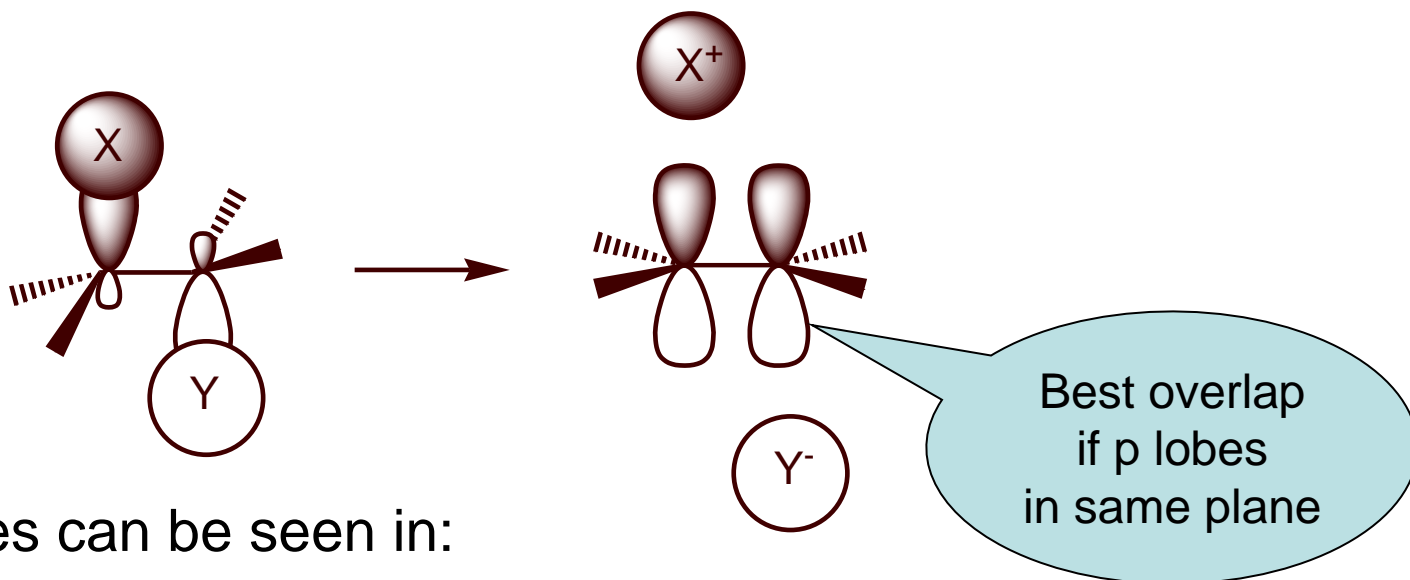
- High degree of polymerisation
  - Rate of internal reaction is very slow
  - Intermolecular reaction becomes competitive
- 9 to 11-membered rings do not form

## The *anti-periplanar* Transition State for E2

The full geometric requirements for E2 are described as *anti-periplanar*:

- X, C, C, Y are in one plane
- X and Y are on opposite sides of the C-C bond

This geometry allows for maximum orbital overlap for formation of the new  $\pi$ -bond:



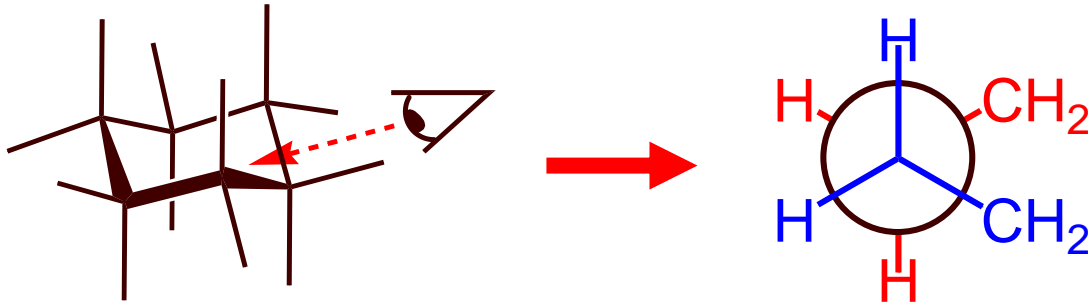
Consequences can be seen in:

- geometry of products
- ease with which the reaction proceeds

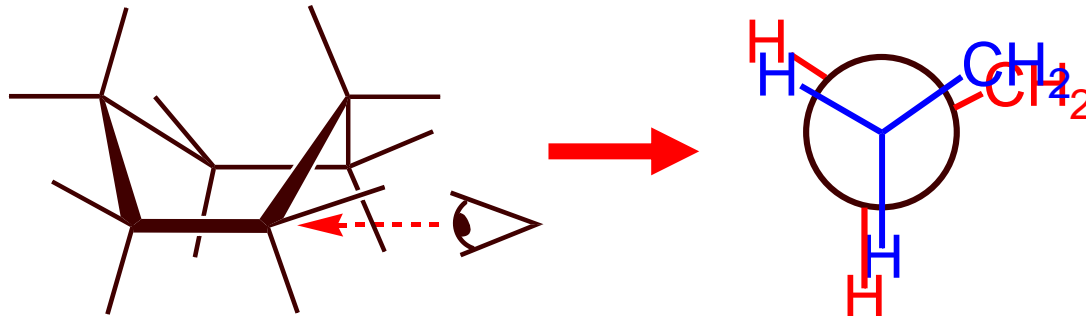


# Newman Projections of Cyclohexane

- chair* form – ideal, all bonds staggered



- boat* - 2 sides with eclipsing bonds



# Exam Tips

- Past papers are always a good idea
- Study now to save work later
- Come and see me if you need help