CHEM202

Stereochemistry

Lecture 2

Cyclisation Reactions

Part 1

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Curl-up

Recap of yesterday…

- Newman projections
- Eclipsed through to staggered conformations
- Ring strain: Torsional, bond angle and van der Waals interactions

Favoured Ring Size Varies

The 6-membered ring is not always the most favoured

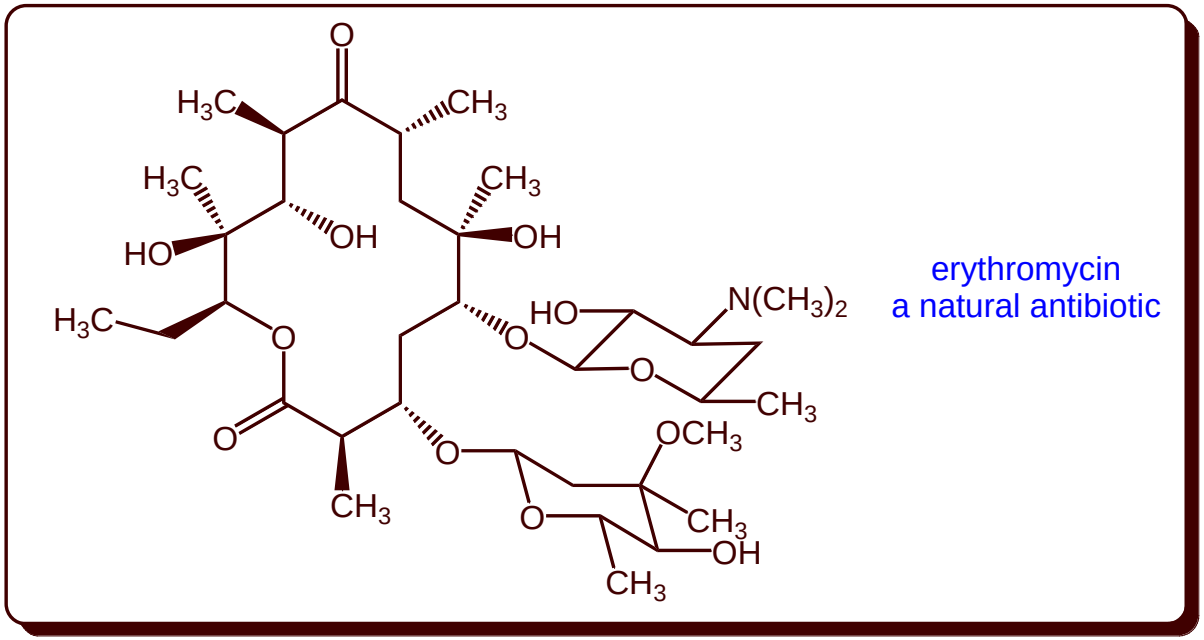
Some influential factors:

- Atoms other than C may have different preferred bond angles
- Divalent ring atoms:
  - have no bonds to become involved in eclipsing
  - have no attached groupings – less van der Waals interaction
  - planar conformations may be feasible
- Interactions between charged or partially charged centres

Molecular modelling is again very helpful

Ring Formation

- Rings of various sizes and compositions are known
- Ring formation is a very important part of synthetic chemistry



erythromycin
a natural antibiotic

- Look at formation of rings from acyclic compounds:
- Key factor – **is the ring formation reversible?**

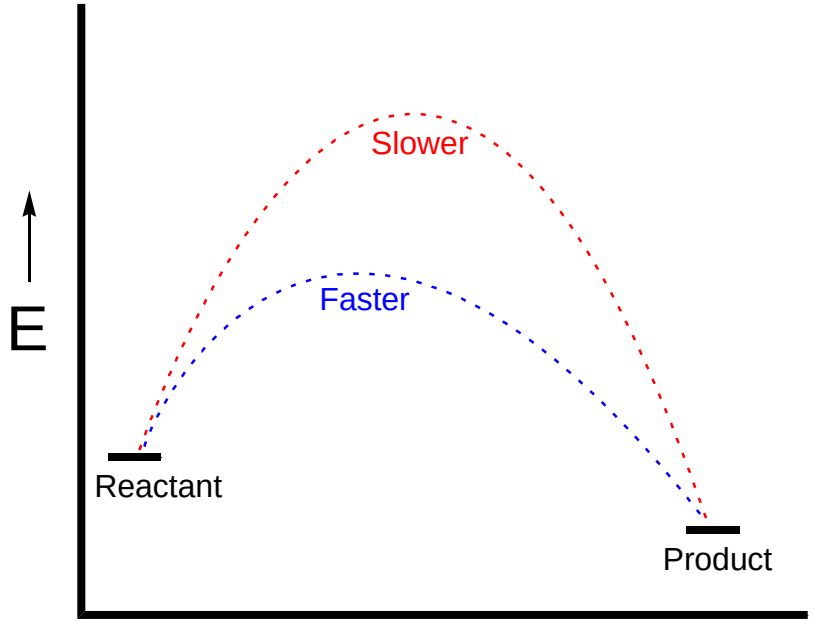
Recap on Substitution Reactions

- Types?
- Mechanistic differences?
- Kinetics
- Substrate scope

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

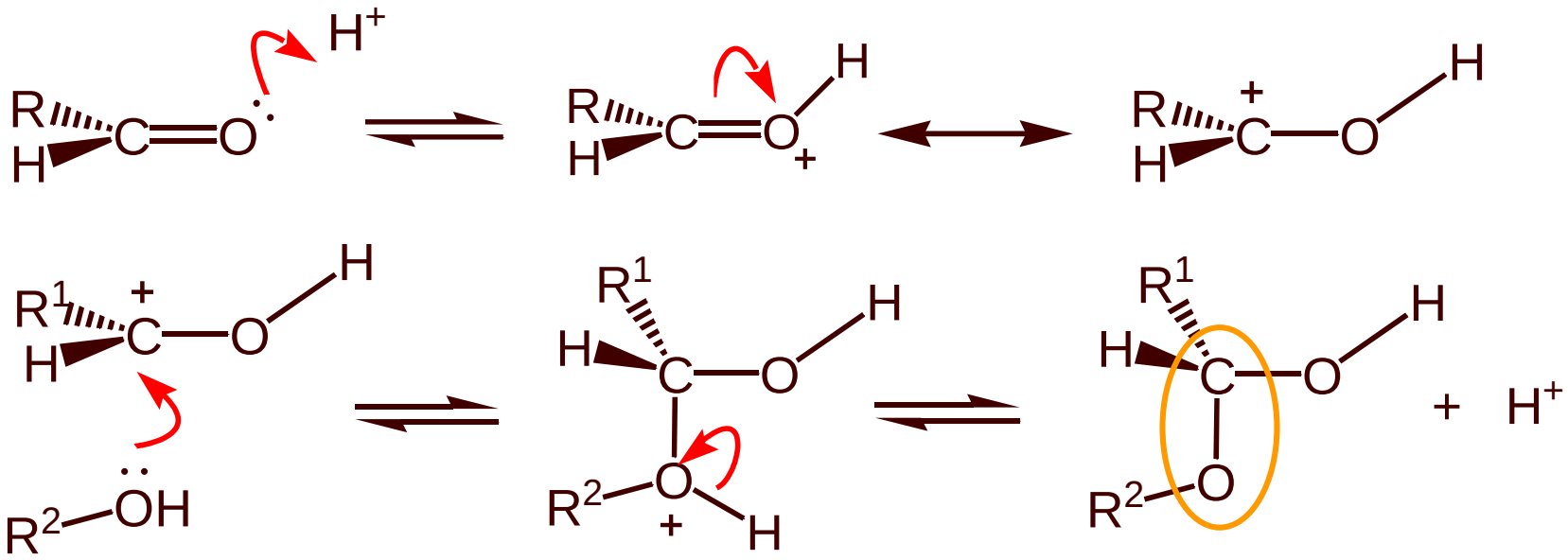


Reversible Ring Formation

- 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

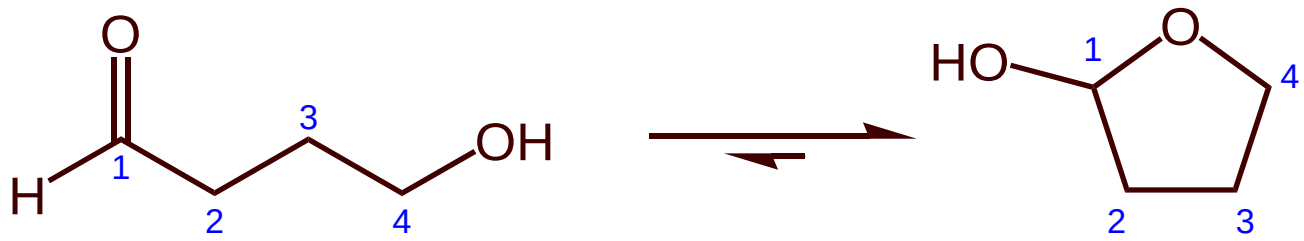
- Results when an alcohol and an aldehyde are treated with acid (CHEM 191)



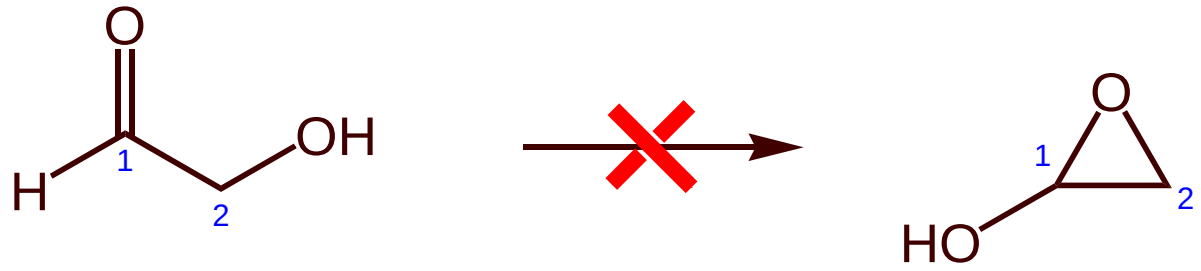
Cyclic Hemiacetal Formation

- If both components are part of the same molecule ⇒ a ring
- Equilibrium only favours cyclized product if the ring is unstrained

A product with a 5-membered ring may be isolated:

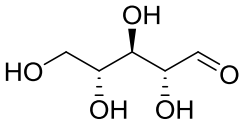


but one with a 3-membered ring cannot:

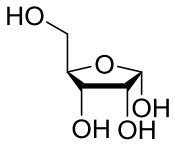


- Hemiacetal rings are very important in carbohydrate chemistry – *e.g.* monosaccharides (CHEM 191):
  - The only significant cyclic species have 5 or 6-membered rings
  - Levels of 3, 4 or 7-membered ring species are negligible

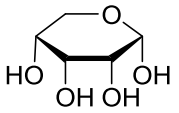
D-Ribose



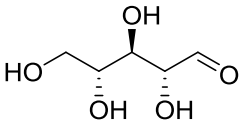
- How many cyclic hemiacetals would you expect to form?

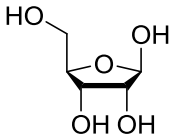


α-D-ribofuranose

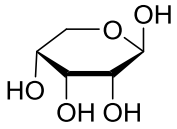


α-D-ribopyranose



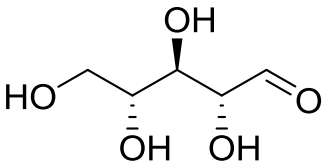


β-D-ribofuranose



β-D-ribopyranose

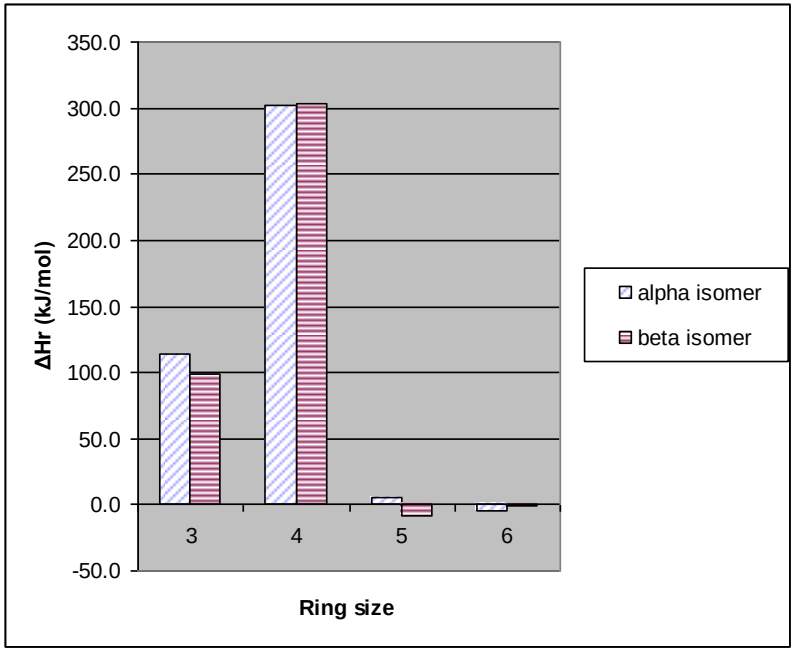
D-Ribose in Water at 25°C



Ribose exists only in *furanose* and *pyranose* forms

As expected from ΔH_r values calculated (ΔH_f (ring) - ΔH_f (acyclic), molecular mechanics) for cyclization to the various ring forms:

Ring size	ΔH_r (kJ/mol) α	β
3	114.1	98.6
4	302.1	303.1
5	6.1	-8.4
6	-4.1	-1.3

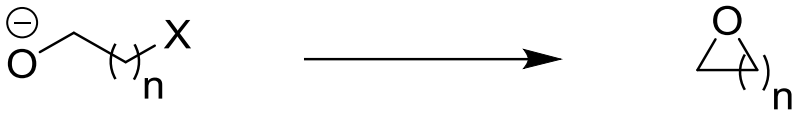


Note:

- Formation of 3 and 4-membered rings is highly endothermic.
- For the 5β, 6α and 6β isomers, ring formation is predicted to be exothermic.
- Calculations are for the gas phase. There will be some differences in water solution.

Cyclic Ethers

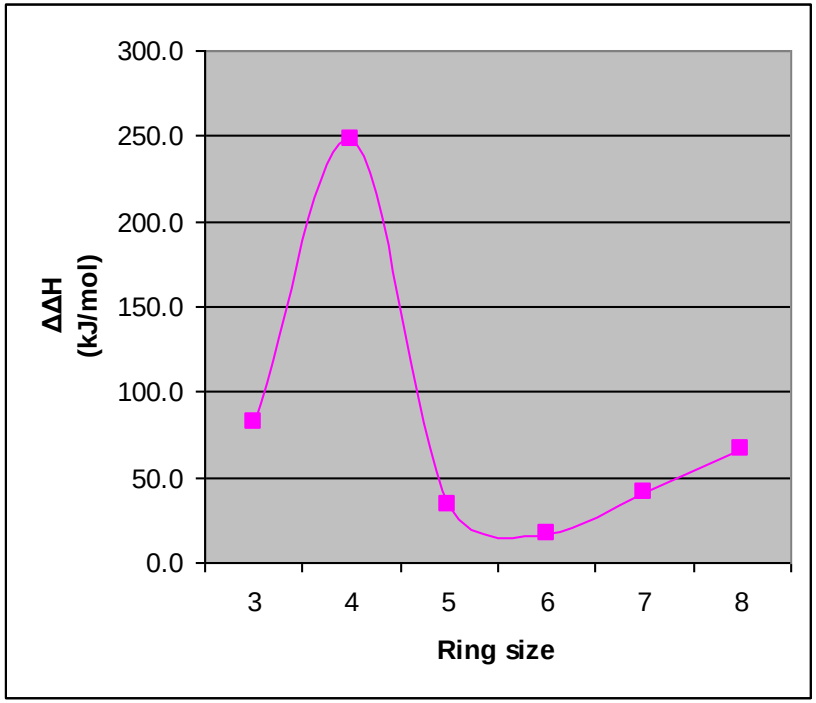
- Alkoxide + alkyl halide $\Rightarrow$ ether (S_N2 reaction – CHEM 191)
- If both functions are part of the same molecule $\Rightarrow$ cyclic ether
- Not reversible - halide ion (nucleophile) cannot displace alkoxide ion (poor leaving group)
- Rate of reaction strongly dependent on ring size. Observations:
  - 3 ≈ 5 > 6 > 4 ≈ 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



Explanation - 1

- The difference in ΔH_f (ΔH_f (ring) - ΔH_f (acyclic)) calculated by molecular mechanics shows the strain present in each of the ring forms:

Ring Size	$\Delta\Delta H_f$ / kJ mol^{-1}
3	82.8
4	248.5
5	33.9
6	17.2
7	41.4
8	66.6

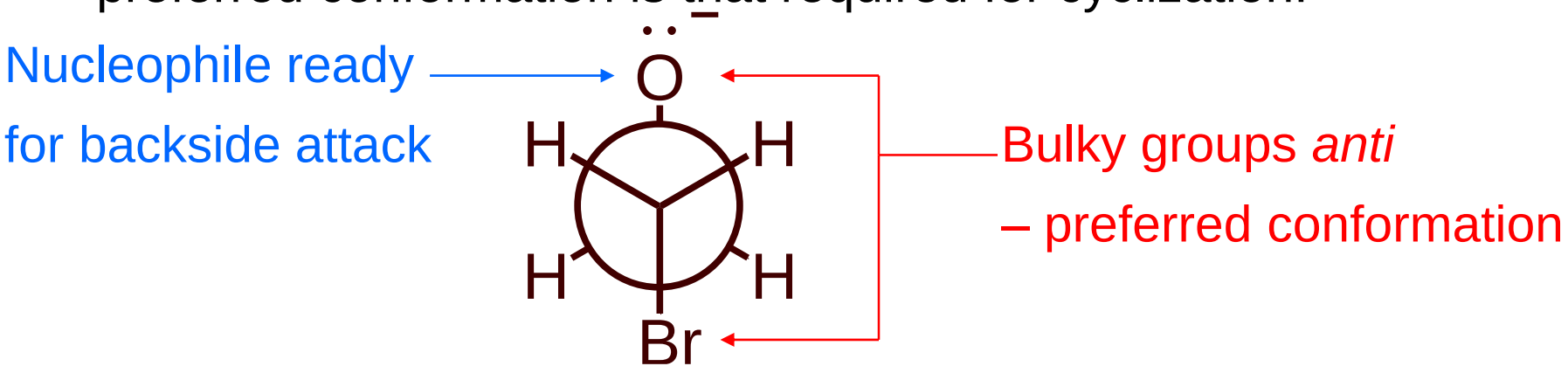


- *i.e.* ring strain preference 6 > 5 > 7 > 8 > 3 > 4

  (*c.f.* observed 3 ≈ 5 > 6 > 4 ≈ 7 > 8)

Explanation - 2

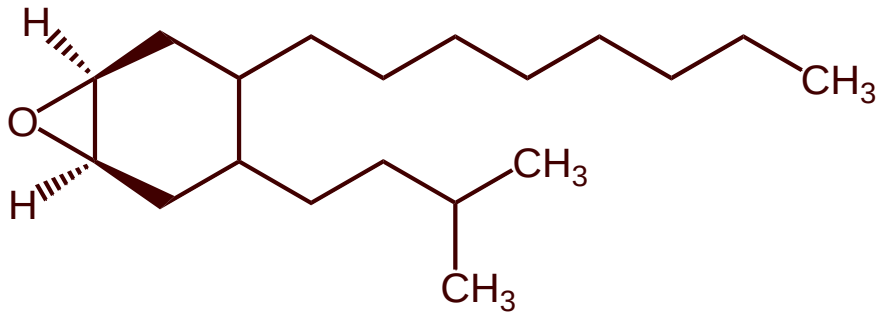
- Must be some additional factor:
  - Relates to the probability of the reacting centres coming together to attain the necessary transition state
  - If no. of intervening bonds is large, this will be low
- With the 3-membered ring, probability is very high – the preferred conformation is that required for cyclization:



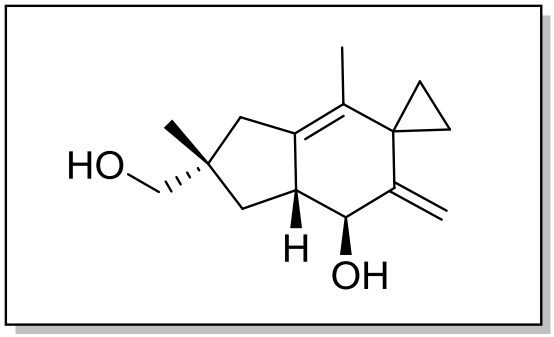
- As the ring size increases, the probability factor becomes less favourable
- Results overall represent a combination of ring strain and probability factors

3-Membered Rings in Natural Products

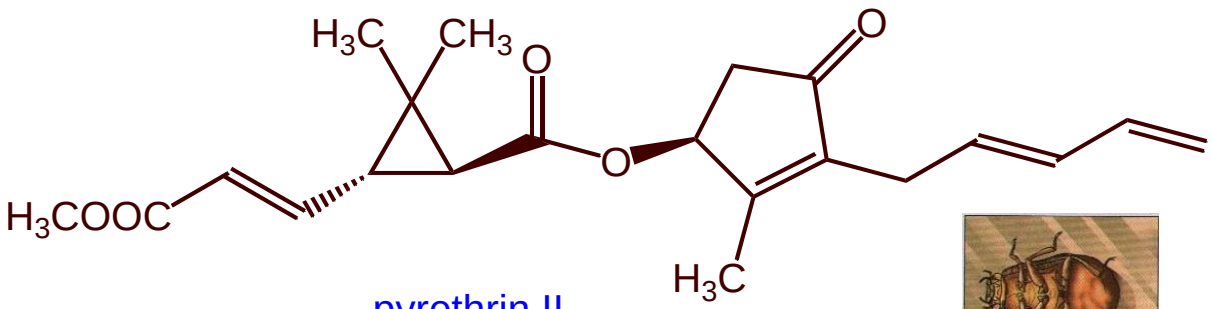
Despite the ring strain, compounds containing 3-membered rings are quite common in nature



disparlure
gypsy moth sex pheremone



Dalmatian Pyrethrum *Tanacetum cinerariifolium*



pyrethrin II
natural insecticide

Lecture Problem

Predict the major product of the following reaction: