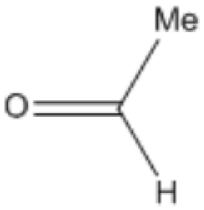
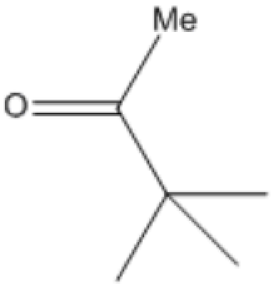
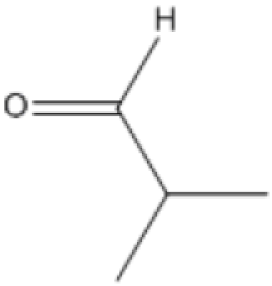
9.1 Nucleophilic Addition to Carbonyl groups: Reactivity

Rank the following compounds in a) and b) from most reactive to least reactive towards nucleophilic addition.

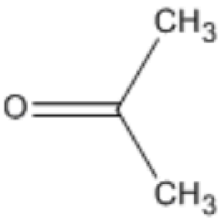
a) On the basis of steric crowding, the first one is most reactive, then the last one, then the middle.

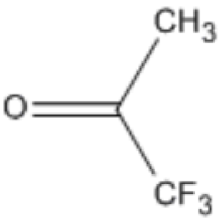


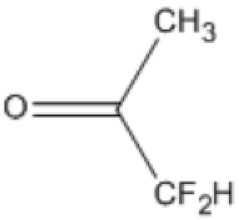




b) On the basis of electronics, the middle one is most reactive, then the last, and then the first. The fluorine atom is very electronegative and pulls electron density towards itself. That leaves more positive charge on the nearby carbonyl carbon. The more fluorines on that nearby carbon, the more positive the carbon. The more positive the carbon, the more it attracts electrons from a nucleophile.

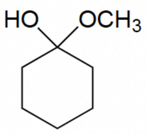


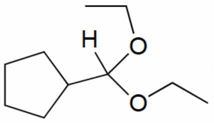


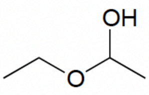


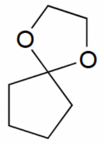
9.2 Acetals and Ketals: Reaction Mechanism

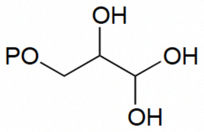
a) Categorize each of the following molecules as a hemiacetal, hemiketal, acetal, ketal, hydrate of an aldehyde, or hydrate of a ketone.


A


B


C


D

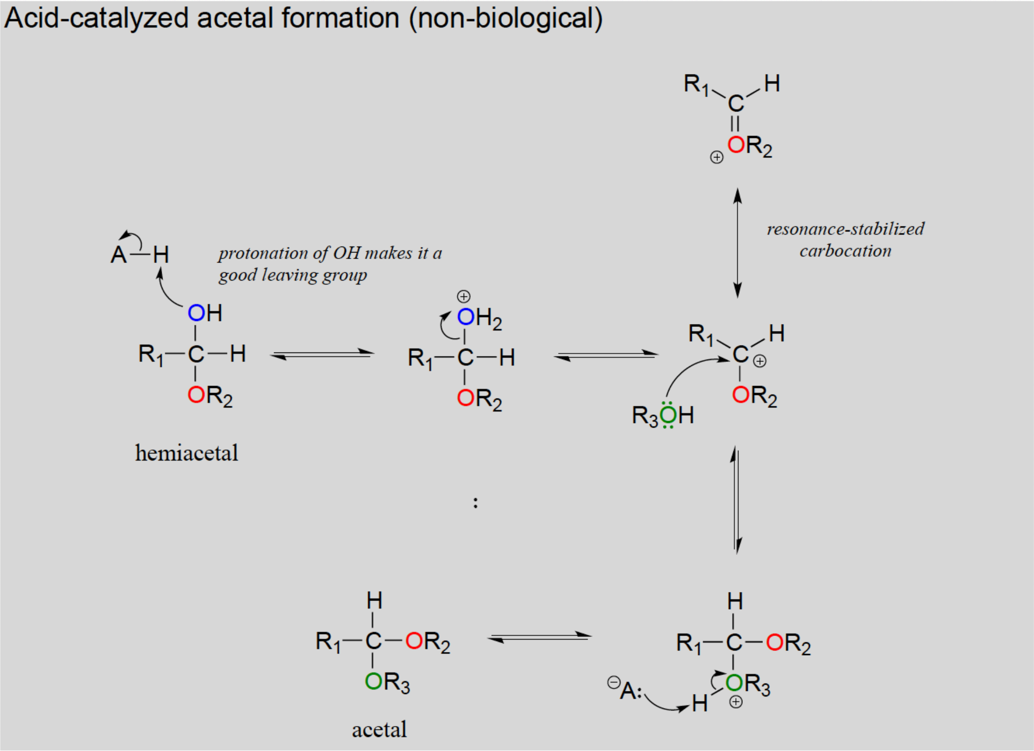

E

A. Hemiketal B. Acetal C. Hemiacetal

D. Ketal E. Hydrate of an Aldehyde

b) Draw the mechanisms for a non-biological acetal formation starting from a hemiacetal catalysed by a strong acid. Does it follow an SN1 or SN2 -type reaction? How do acetal formation in a biochemical context differ from the acid catalyzed acetal formation?

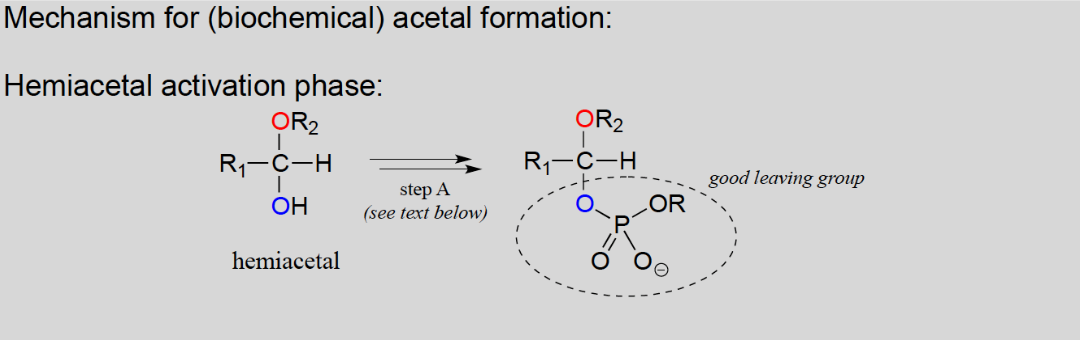
I. Acid catalyzed:



The reaction follows an **SN1 type** mechanism, where in the first step the hydroxyl group gets transformed into a good leaving group by protonation.

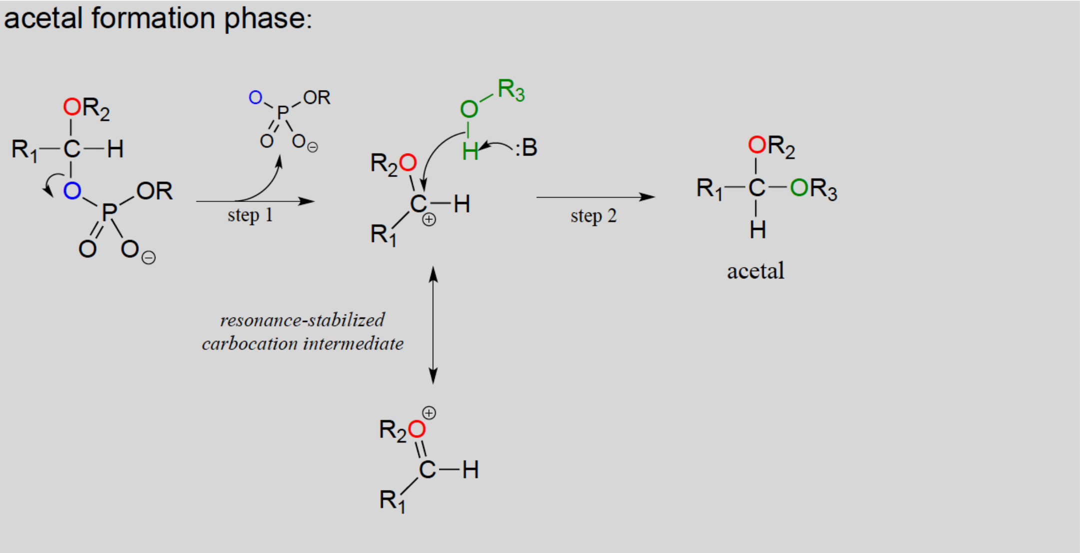
In a biochemical context, the hydroxyl group gets converted into a good leaving group by other means than protonation. It involves phosphate group transfer steps that are familiar from chapter week 7.

For reference see lecture 8, slides 29&30 or For reference see Organic Chemistry With a Biological Emphasis Tim Soderberg Chapter 10, p 67:



Mechanism for (biochemical) acetal formation:

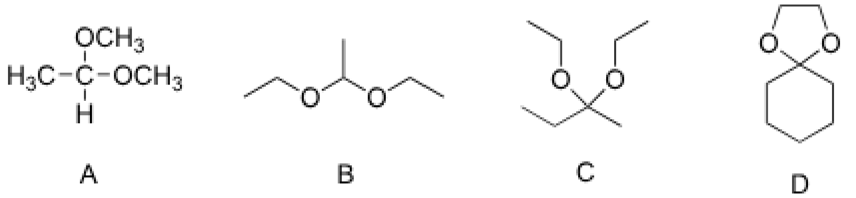
Hemiacetal activation phase:

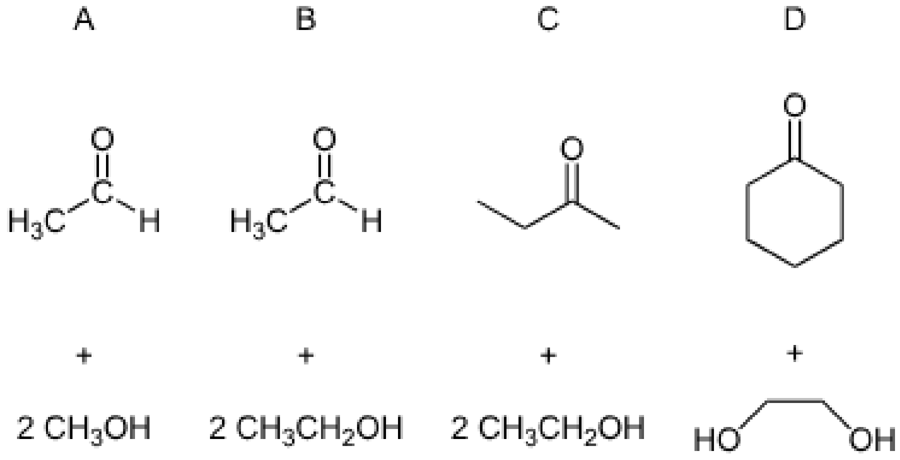


acetal formation phase:

9.3 Acetal/Ketal Formation

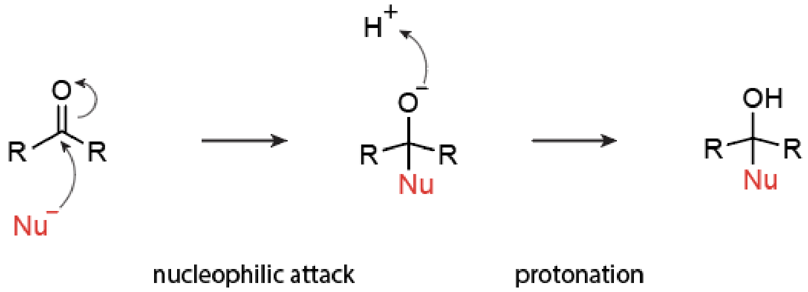
For each acetal/ketal A-D in the figure below, specify the required aldehyde/ketone and alcohol starting materials.



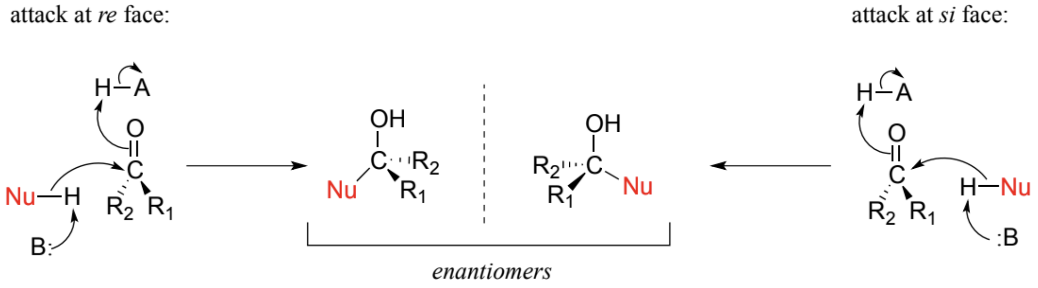


9.4 Nucleophilic Additions to Carbonyls: Reaction Mechanism

a) Draw the steps of a nucleophilic addition to a carbonyl. Use arrows to indicate the movement of electrons.



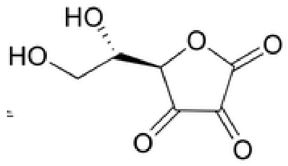
b) Assuming that R1 and R2 are non-identical substituents, which enantiomer(s) do you expect for the addition reaction of the following educts?



As we have seen in 8.1 carbonyls are trigonal planar. The nucleophilic attack of the nucleophile (abbreviated Nu) can occur either from the re face or si face (in the schematic drawing above the priorities are assumed to be: $R_1 > R_2$). Thus, the resulting product will be a 50/50 mixture of the two enantiomers (racemate).

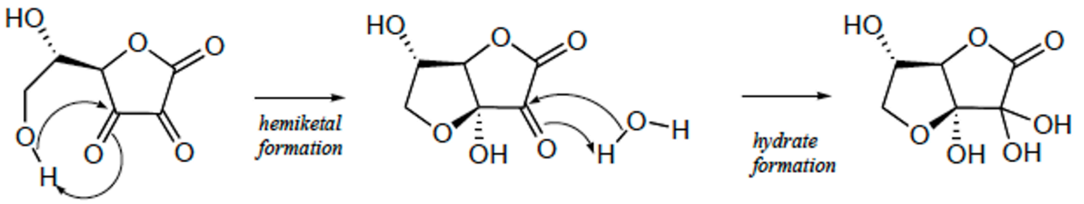
9.5 Nucleophilic Additions to Carbonyls

You probably know that ascorbic acid (vitamin C) acts as an antioxidant in the body. When vitamin C does its job, it ends up being oxidized to dehydroascobate, which is usually drawn as shown below, in the so-called tricarbonyl form.



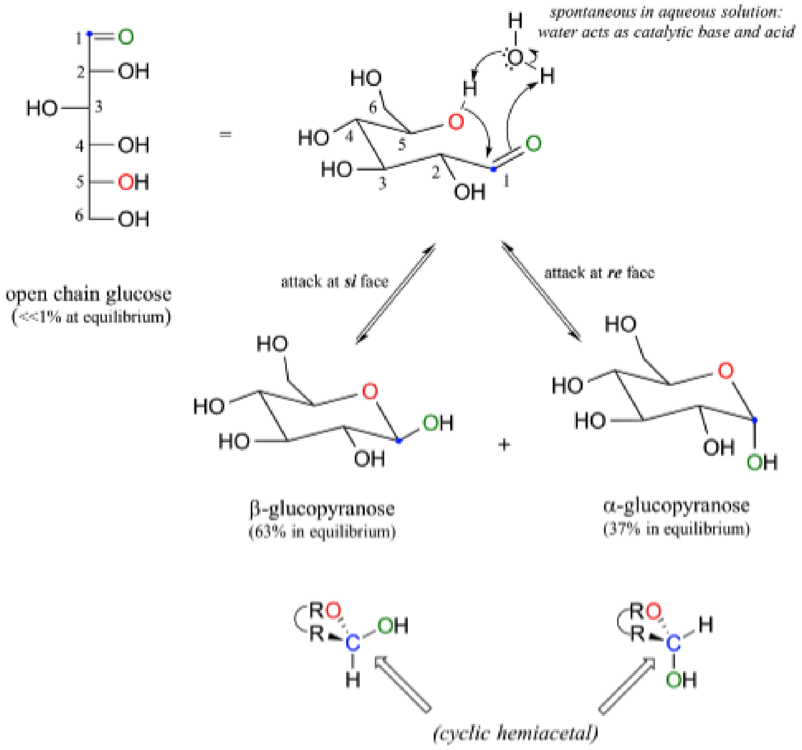
dehydroascorbate
(tricarbonyl form)

Evidence suggests, however, that the most important form of dehydroascorbate in a physiological context is one in which one of the ketone groups is in its hydrated form, and the other is an intramolecular hemiketal (see Chemical and Engineering News, Aug. 25, 2008, p. 36). Show the structure of this form of dehydroascorbic acid.



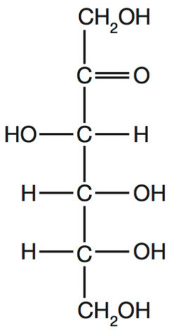
9.6 Aldoses and Ketoses: hemiacetals and hemiketals of sugars

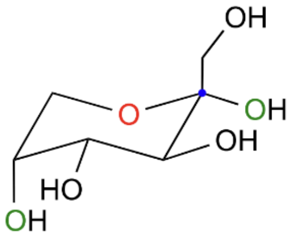
a) Sugars can form intramolecular hemiacetals or hemiketals. Draw the resulting 6-ring structure after an intramolecular nucleophilic attack in glucose. What are anomers and how do they form? Reason which anomer is more prevalent in solution? Glucose is shown in its Fischer-Projection below. The numbers 1-6 indicate the carbons. The alcohol highlighted will attack the aldehyde. Hint: glucose in its circular structure will adopt a chair conformation in 3D space.



The anomers result from the nucleophilic attack occurring from the re or si face of the carbonyl group. The hydroxyl group is either axial (alpha) or equatorial (beta). The equatorial position is energetically favourable and thus more prevalent.

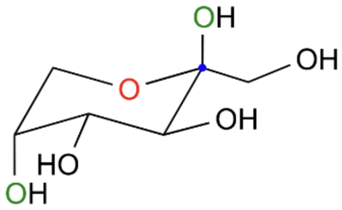
b) In solution, fructose is present in a 5-ring and 6-ring structure. Draw the cyclic structures of fructose. Which ring structure is more common in solution? Why?



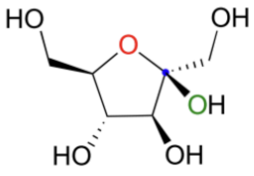


α-fructopyranose (~1%)

+

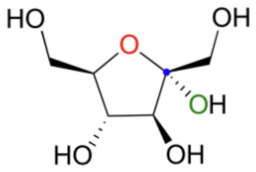


β-fructopyranose (70%)



β-fructofuranose (23%)

+

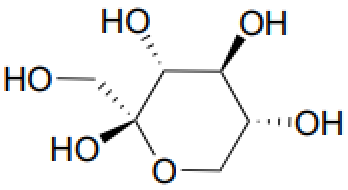


α-fructofuranose (5%)

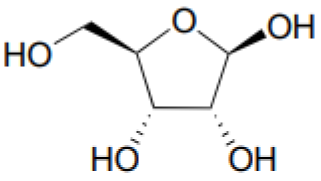
The 6-membered ring (pyranose) is more prevalent due to lower energy (less ring strain than in 5-ring furanose forms)

9.7 Sugar chemistry

a. Identify the anomeric carbon of each of the sugars shown below.



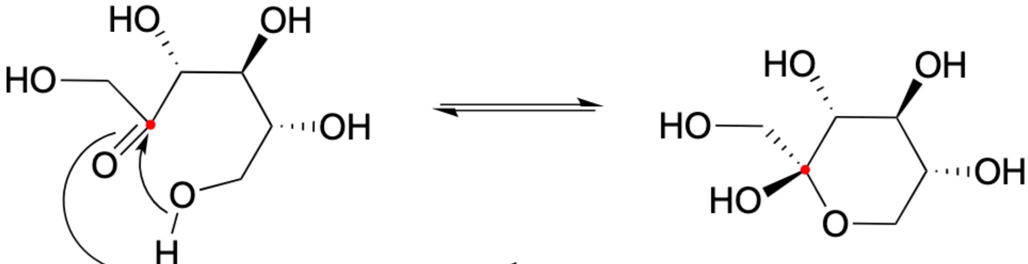
sorbose



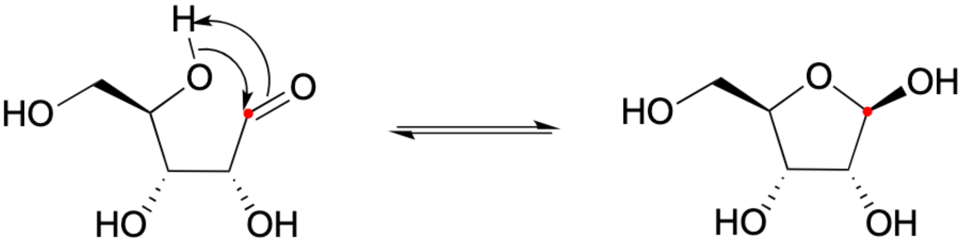
ribose

b. Draw mechanisms for cyclization of the open-chain forms to the cyclic forms shown.

The anomeric carbon is indicated by a solid (red) dot.



sorbose



ribose

9.8 Nucleophilic Addition of Water

Draw for the nucleophilic addition of water to acetone and to formaldehyde the corresponding equilibrium reactions. Which reaction yields more of the hydrate form at equilibrium and why?

Formaldehyde is more readily attacked by water due to less steric hindrance than acetone. The equilibrium lies strongly on the side of formaldehyde hydrate.