Reactions of Alcohols

Answers and Explanations

1. A

The conversion of ethanol into acetaldehyde is an oxidation. As a consequence of the reaction, two electrons pass from ethanol to NAD^+, the oxidizing agent. The ethanol dehydrogenase mechanism, in other words, leads to production of NADH in the cytosol. This makes conditions in the cytosol too reducing. (It's important to understand that just like conditions in the cell can be acidic or basic based on the degree of protonation of solution components, an enviornment may be oxidizing or reducing based on the oxidation state of components.) Cytosol with a higher than normal NADH concentration is a reducing environment. Think of being within a reducing environment as a kind of 'electron pressure' onto the components of the solution. This is what happens to pyruvate in this case. Among other effects, the reducing environment produced by a great deal of ethanol dehydrogenase activity in the cytosol leads to reduction of pyruvate, transforming it into lactate. Thus, one of the effects of excessive alcohol consumption is inhibition of gluconeogenesis in liver cells.

2. A

When you have the structural formula of an organic compound, assign oxidation numbers by deciding which atom has 'control' of the electrons in the bonds. Control goes to the more electronegative atom.

The carbon of a primary alcohol gains two electrons that the two hydrogens brought and loses one to oxygen, so the oxidation state of the hydroxyl carbon at the start is –1.

After the reaction, the carbon will now have three electrons invested in bonds to oxygen (a double bond and a single bond), so its oxidation state in the histidine α carboxyl group has become +3. It has been oxidized by $2NAD^+$ in a four electron transfer.

3. C

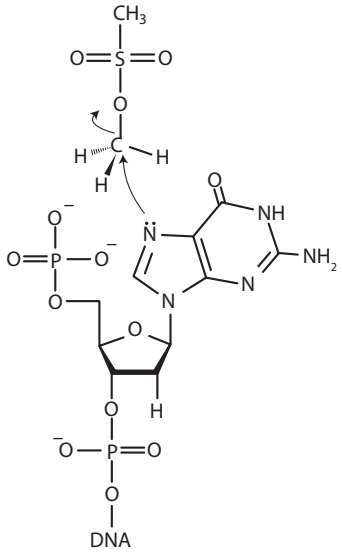
The threonine hydroxyl group is a somewhat less apt nucleophile for SN2 substitution because it is more hindered. (It also has a slightly *higher* pK_a, so it spends less time in the more reactive deprotonated form.)

4. D

As a figure of merit for MCAT preparation, the important thing for this question would be to recognize the mesylate leaving group in the structure of the reagent.

The reagent could have been formed by a prior treatment of methanol with methanesulfonyl chloride to convert the hydroxyl of methanol into a leaving group. Mesylate is an excellent leaving group in nucleophilic substitution reactions because the negative charge on the leaving group is stabilized by resonance.

Being a good substrate for SN2 substitution makes our reagent a tool for the convenient methylation of a nucleophlic moeity.



5. B

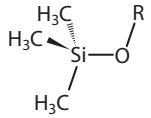
When you have the structural formula of an organic compound, assign oxidation numbers by deciding which atom has 'control' of the electrons in the bonds. Control goes to the more electronegative atom.

The carbon of a secondary alcohol gains one electron from a hydrogen and loses one to oxygen, so the oxidation state of the hydroxyl carbon at the start within 3-phosphoglycerate is 0.

After the reaction, the carbon will now have two electrons invested in its double bond to oxygen, so its oxidation state in 3-Phosphohydroxypyruvate has become +2.

6. A

TMSO stands for tetramethylsylyl ether.

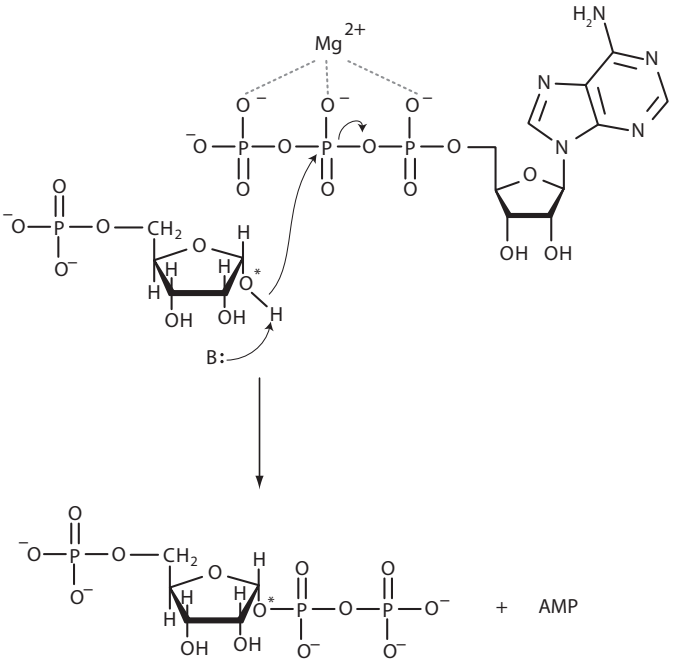


Silylating agents are often used in synthetic organic chemistry to protect hydroxyl groups from adverse reaction conditions. In the role of protection, they group forms a silyl ether with the substrate. Silyl groups are particularly useful for this purpose because they can be installed and removed very selectively under mild conditions.

7. A

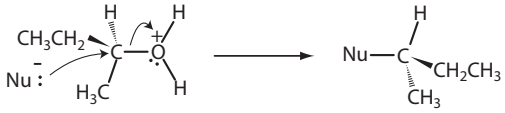
You will often see a hydroxyl group serving as the target of phosphoryl transfer in biochemistry. Because the hydroxyl group serves as the nucleophile in a phosphoryl transfer reaction, it is the same extracyclic oxygen on the anomeric carbon in phosphoribosyl pyrophospate after the reaction as had been in that location prior to the reaction in ribose-5-phosphate.

Note that transfer of pyrophosphate is very similar to what occurs in serine, threonine or tyrosine kinase except that the attack by hydroxyl occurs on the β phosphate of ATP, transfering a pyrophosphate, instead of on the γ phosphate of ATP in a kinase.

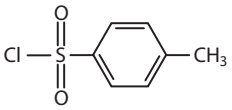


8. C

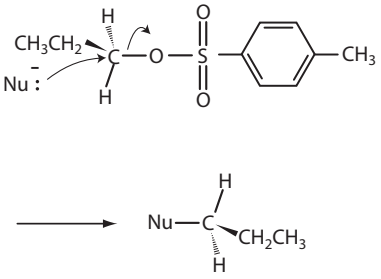
It is a very important thing about the hydroxyl group to understand that it is a *very poor leaving group*. One way to get a hydroxyl group to leave is by acid catalysis. This way it can leave as water.



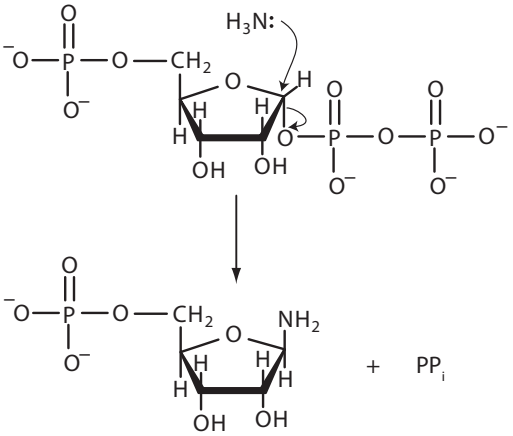
This is *p*-toluenesulfonyl chloride:



p-Toluenesulfonyl chloride can transfer its toluenesulfonyl moeity onto a hydroxyl group, transforming the hydroxyl group into a tosylate. Due to resonance stabilization, this an excellent leaving group.



p-toluenesulfonyl chloride does does appear on the life sciences benchtop, in drug synthesis, for example. However, it's more likely that AAMC decided to include the reagent on the MCAT outline because there are so many instances in biochemistry with the same logic involving ATP (or UTP). In purine biosynthesis, transfer of pyrophosphate onto ribose-5-phosphate transforms the C1 hydroxyl group into great leaving group.

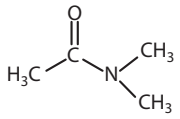


9. B

Student A would be correct for a benchtop reaction but not for a biochemical reaction. On the benchtop, absent a very special catalyst, stereospecific inversion of configuration with these reagents would be unequivocal evidence of SN2 substitution. However, enzyme catalysis is capable of producing stereospecific configurations through addition to a planar, achiral carbon. This is because the substrates are bound with multiple points of attachment within an active site that is itself asymmetric. It happens all the time in biochemistry that a pure optical isomer derives from an achiral, planar precursor. Even though the mechanism here *actually is* SN2 substitution, student B is correct that the inversion of configuration on its own is not enough evidence.

10. C

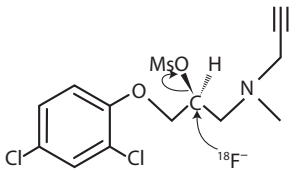
Dimethylacetamide (DMA) is a polar aprotic solvent. While having a high dielectric constant (polar), it does not possess any hydrogens bonded to electronegative elements, such as in hydroxyl or amine groups.



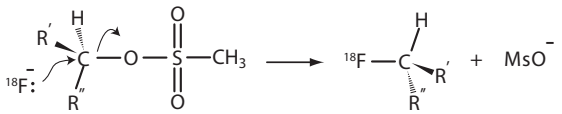
Polar aprotic solvents are the optimal type of solvent for SN2 substitution. Their dielectric property helps stabilize the charge separations of the transition state, but unlike a protic solvent, they don't carry out the hydrogen bonding that would cage and over-stabilize the nucleophile.

11. D

Steps 4 has SN2 substitution on a chiral center.

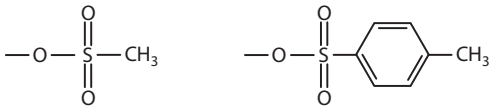


SN2 substitution leads to inversion of configuration. While Steps 1 and 2 are also SN2 substitution, inversion of configuration is only stereochemically dispositive with a chiral center.



12. D

The hydroxyl group is a poor leaving group. A solution to the problem is to turn the alcohol into a sulfonic ester. A commonly employed method is to form an organic mesylate or an organic tosylate by treatment of the alcohol with either methanesulfonyl chloride or para-toluene sulfonyl chloride. Mesylate (-OMs) and tosylate (-OTs) groups are excellent leaving groups in nucleophilic substitution reactions because the negative charge on the leaving group is stabilized by resonance.



Mesylate (-OMs)

Tosylate (-OTs)

13. C

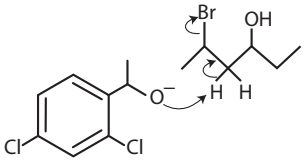
Sodium hydride (NaH) is is a very strong base (a superbase) capable of deprotonating even very weak Brønsted acids. NaH has utility in organic chemistry where typical substrates contain O-H, N-H, S-H bonds. The abstraction of the proton from 2,4-dichlorophenol in Step 1 of our synthesis converts the molecule into a phenolate anion, being charged, a much more aggressive nucleophile (choice II) for SN2 substitution.

Additionally, the basicity of NaH is driven by the high reduction potential of the hydride ion (H^-). Hydride reduces the abstracted proton yielding H_2 (choice IV).

$$H^- + H^+ \rightharpoonup H_2$$

14. B

Abstraction of a proton by NaH from our new reagent yeilds an alkoxide anion, which is a much stronger base than the phenolate anion, a weak base, produced in the original reaction. The favored reaction with a hindered strong base, especially with a secondary alkyl halide, will be E2 elimination, not SN2 substitution.



Note that the proton taken by the base is the one which produces the most highly substituted alkene (so not a proton from the end carbon).