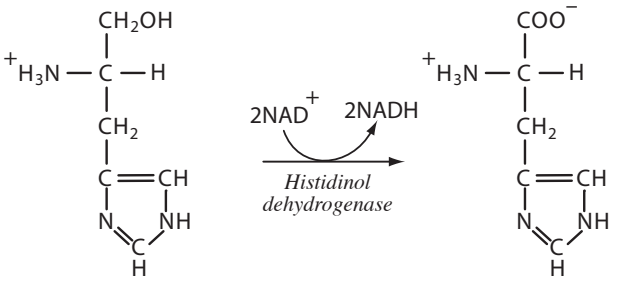
Reactions of Alcohols
Practice Items

1. Ethanol is metabolized to acetaldehyde in the cytosol of liver cells by alcohol dehydrogenase. Consumption of ethanol in excess can disregulate cellular metabolism by inhibiting gluconeogenesis and promoting fatty acid synthesis by making conditions in the cytosol too . . .

A. reducing
B. oxidizing
C. acidic
D. basic

2. Histidinol dehydrogenase is the final step in histidine biosynthesis.



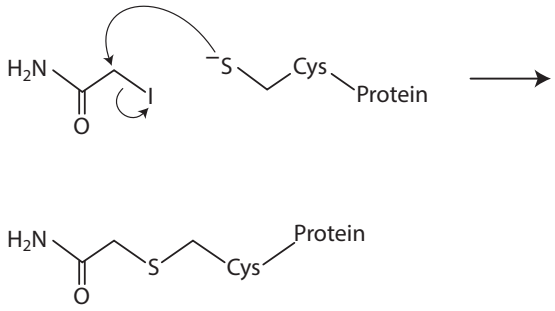
L-Histidinol Histidine

What change has occurred to the oxidation state of the hydroxyl bearing carbon of histidinol as a result of this reaction?

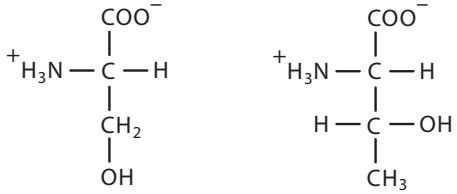
A. –1 → +3
B. 0 → +3
C. 0 → +4
D. +1 → –3

3. 2-Iodoacetamide is an alkylating agent used for peptide mapping purposes. It binds covalently with the thiol groups of cysteine residues preventing the formation of disulfide bonds. 2-Iodoacetamide may also be utilized as an irreversible inhibitor of enzymes, such as glyceraldehyde-3-phosphate dehydrogenase, that employ a reactive cysteine in their mechanism.

The figure below depicts the alkylating mechanism of 2-iodoacetamide.



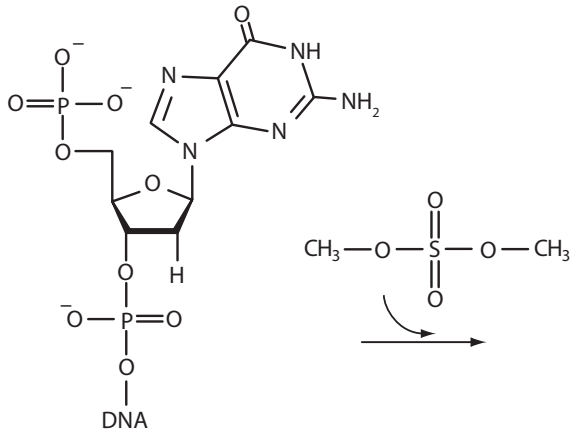
Tthe alkylation may also occur at other locations in undesireable side reactions including upon N-terminal serines or threonines with the former more apt to occur. Which of the following describes one of the reasons that serine residues are more likely to undergo alkylation than threonine residues?



Serine Threonine

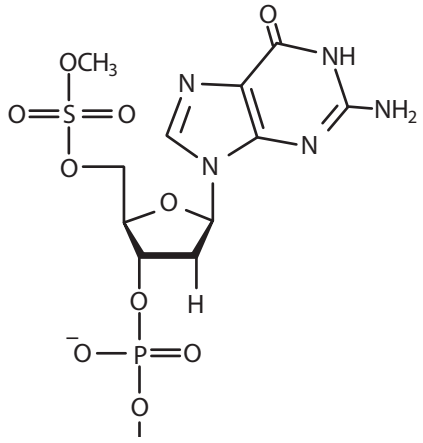
A. The hydroxyl group is a poorer leaving group from threonine than serine.
B. Carbocation formation is more likely to occur with threonine than with serine.
C. The serine hydroxyl group is less hindered than the threonine hydroxyl group.
D. The hydroxyl group of serine has a higher pK_a than that of threonine.

4. Below is the first step in the chemical cleavage method of DNA sequencing developed by Maxam and Gilbert.

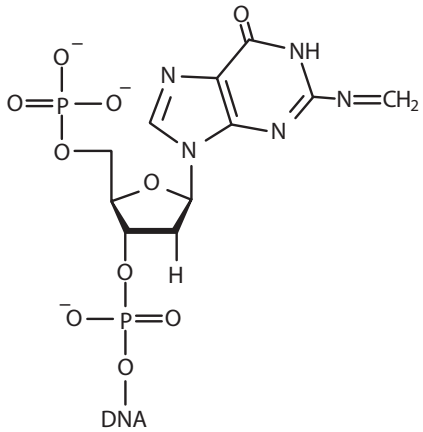


Which of the following structures represents the product of this reaction?

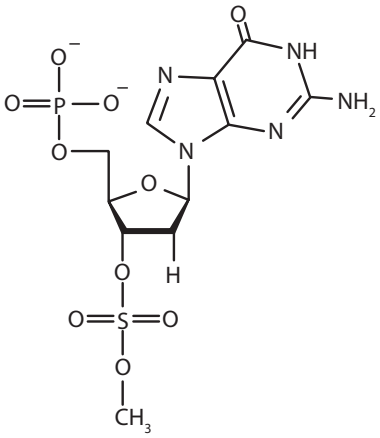
A.



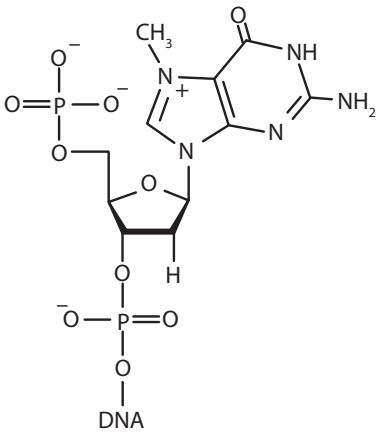
B.



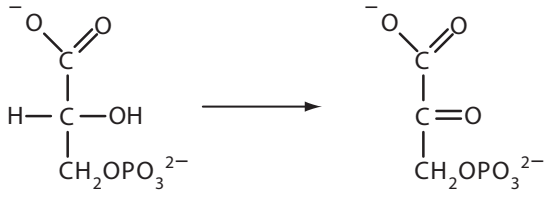
C.



D.



5. 3-phosphoglycerate dehydrogenase is a step in serine biosynthesis.

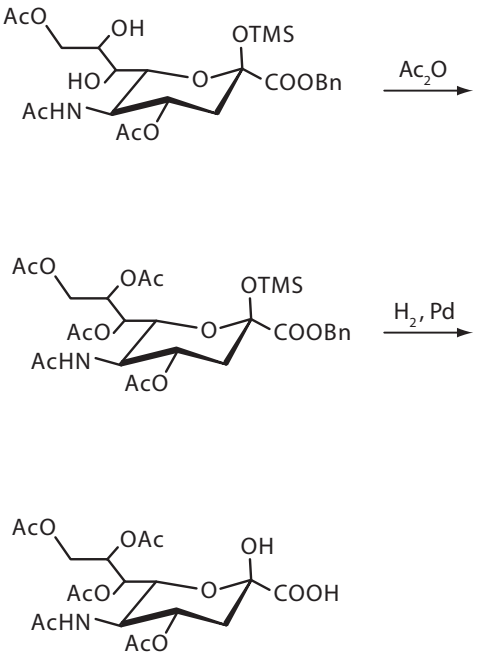


What change has occurred to the oxidation state of the hydroxyl bearing carbon of 3-phosphoglycerate as a result of this reaction?

A. −1 → +2
B. 0 → +2
C. 0 → +4
D. +1 → +2

6. Because postglycosylation acetylation of sialic acid is important to virus pathogenesis and mammalian immune response, the structural and functional understanding of these analogues is an area of active reasearch. Techniques for benchtop synthesis would afford the corresponding sialic acid analogues as useful research tools. This is one of the applications that make methodologies for selective modification of carbohydrate alcohols important synthetic tools in organic chemistry.

The figure below shows the final steps in a synthetic route to 5-N-Acetyl-4,7,8,9-tetra-O-acetylneuraminic acid.

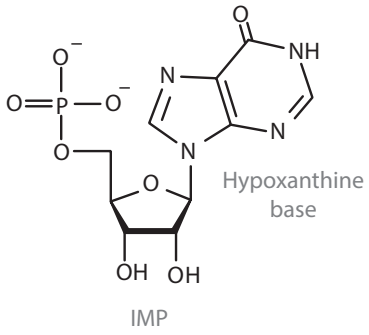


OTMS in the figure above represents . . .

A. **a** silyl ether
B. **a** sulfonic ester
C. **a** mercaptan
D. **a** purine

The following passage pertains to questions 7 - 9.

Bioynthesis of both of the purine ribonucleotides found in RNA, AMP and GMP, begins with a common pathway – the synthesis of inosine monophosphate from the starting material α-ribose-5-phosphate. α-Ribose-5-phosphate is a product of the pentose phosphate pathway.

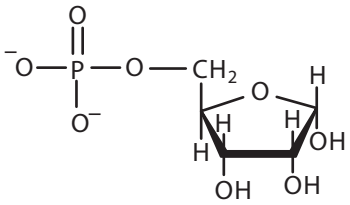


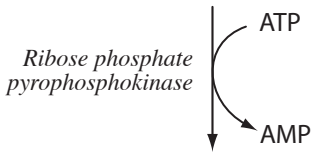
IMP

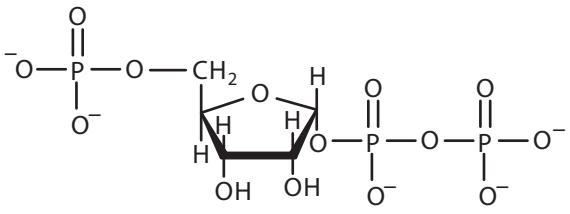
The pathway from α-ribose-5-phosphate to IMP is comprised of 11 steps. The first two steps are shown in the figure at right.

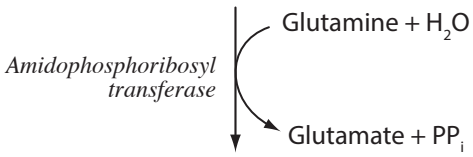
In the first step of IMP synthesis, ribose phosphate pyrophosphokinase reacts α-ribose-5-phosphate with ATP to form 5-phosphoribosyl-α-pyrophosphate (PRPP). A pyrophosphoryl group is transfered to the C1 carbon of ribose-5-phosphate.

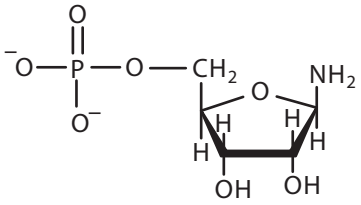
In the second step, amidophosphoribosyl transferase catalyzes the conversion of 5-phosphoribosyl-α-pyrophosphate (PRPP) into 5-phosphoribosyl-β-amine (PRA), using the amine group from a glutamine sidechain. Amidophosphoribosyl transferase possesses two catalytic domains: a glutaminase domain that produces ammonia from glutamine by hydrolysis and a phosphoribosyltransferase domain that binds the ammonia to ribose-5-phosphate. Besides having their respective catalytic abilities, the two domains coordinate with one another to ensure that all the ammonia produced from glutamine is transferred to PRPP and no other nucleophile than ammonia attacks PRPP. This is achieved mainly by blocking formation of ammonia until PRPP is bound and channelling the ammonia to the PRTase active site.

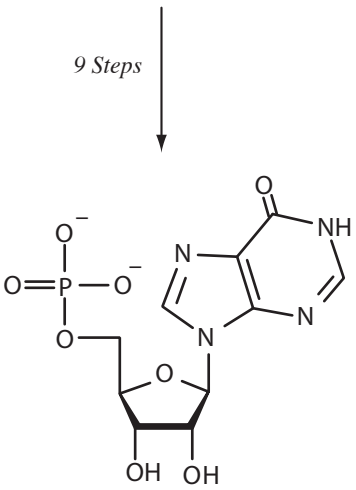












7. A researcher carried out the phosphate pyrophosphokinase reaction with [1-^{18}O]ribose-5-phosphate and ATP in the reaction vessel. The reaction was run to completion. The PRPP product was isolated successfully and mass spectroscopy carried out. The mass spectrum fingerprint of the PRPP obtained showed

A. pure ^{18}O labeled PRPP
B. pure unlabeled PRPP
C. a mxture of labeled and unlabeled PRPP in 1:1 ratio
D. a mixture with unlabeled PRPP predominating

8. The role ATP plays in 'activating' ribose-5-phosphate in purine biosynthesis is most like a common benchtop purpose of which reagent?

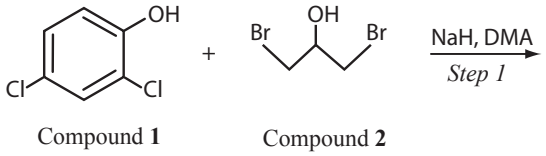
A. trimethylsilyl chloride
B. geranyl pyrophosphate
C. ***p***-toluenesulfonyl chloride
D. pyridinium chlorochromate

9. Based on reagent vs. product stereochemistry, Students A, B, C, & D debated whether the amidophosphoribosyl transferase reaction occurs via SN1 or SN2 mechanism. Student A argued that evidence for SN2 was unequivocal due to the inversion of configiburation at C1. Student B countered that SN1 mechanism might be capable of producing a stereospecific result in the biochemical context. Student C argued for competing reactions consistent with the weak nucleophile. Student D argued that neither SN1 nor SN2 would describe the mechanism but imine formation instead. Which student is correct?

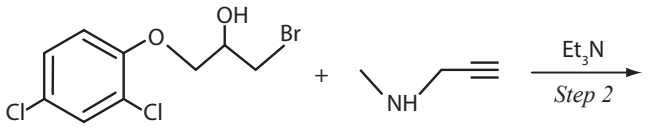
A. Student A
B. Student B
C. Student C
D. Student D

The following passage pertains to questions 10 - 14.

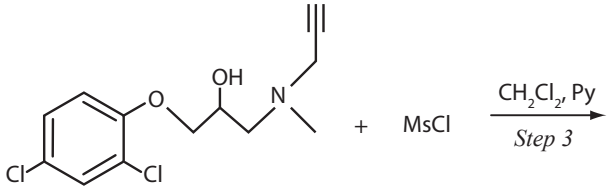
Chemists devised a synthesis of N-[3-(2',4'-dichlorophenoxy)-2-^{18}F-fluoropropyl]-N-methylpropar gylamine (^{18}F-fluoroclorgyline) as a potential positron emission tomography (PET) radiotracer for monoamine oxidase A (MAO-A).



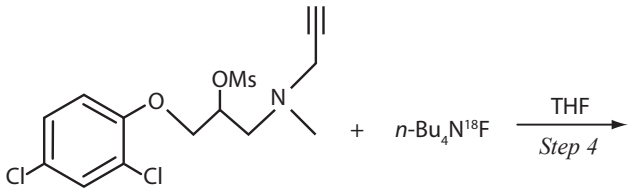
Compound **1** Compound **2**



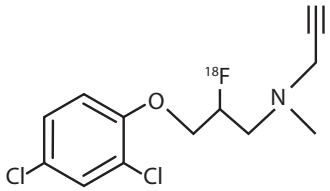
Compound **3** Compound **4**



Compound **5** Compound **6**



Compound **7** Compound **8**



18F-fluoroclorgyline

10. Which is the best description of the dimethylacetamide (DMA) solvent utilized in Step 1?

A. nonpolar
B. protic
C. aprotic
D. aromatic

11. Which step in the spathway includes the inversion of the configuration of a chiral center?

A. Step 1
B. Step 2
C. Step 3
D. Step 4

12. What is the rationale of Step 3?

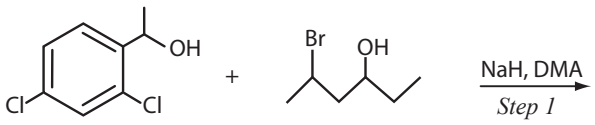
A. ensuring that synthesis is regiospecific
B. protecting the hydroxyl group from oxidation to a carbonyl group
C. preventing formation of precipitate
D. transforming the hydroxyl group into a good leaving group

13. Which of the following results from the action of NaH in Step 1?

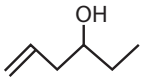
I. acid catalysis
II. activation of the nucleophile
III. stabilizing the transition state
IV. production of H_2 gas

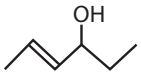
A. I only
B. I and II
C. II and IV
D. I, II, and III

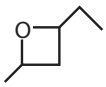
14. The alternative reagents shown below were utilized in an attempt to carry out a variation of the reaction in Step 1:

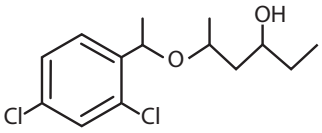


The product was quenched with acid and purified of residual 1-(2,4-dichlorophenyl)ethanol. What was the major product obtained?

A. 

B. 

C. 

D. 

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

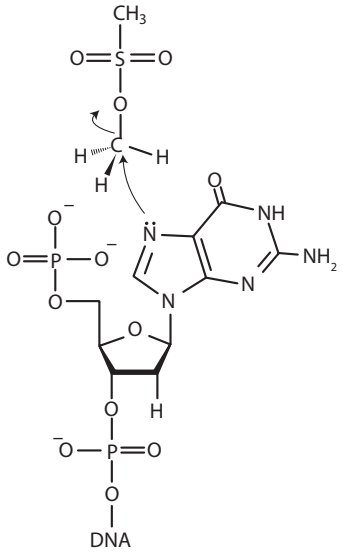
The threonine hydroxyl group is a somewhat less apt nucleophile for SN2 substitution because it is more hindered. (It also has a slightly *higher* pK_a, so it spends less time in the more reactive deprotonated form.)

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

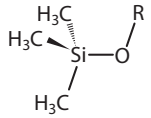
When you have the structural formula of an organic compound, assign oxidation numbers by deciding which atom has 'control' of the electrons in the bonds. Control goes to the more electronegative atom.

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.

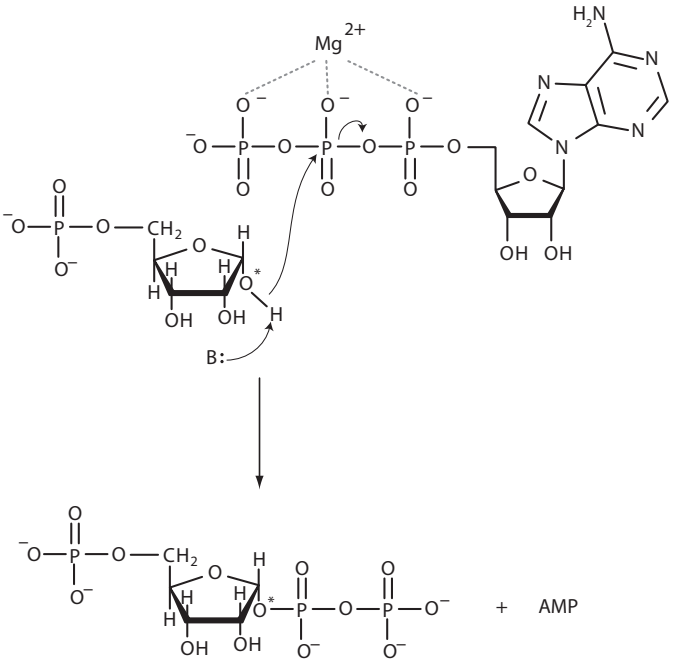


Silylating agents are often used in synthetic organic chemistry to protect hydroxyl groups from adverse reaction conditions. In the role of protection, they group forms a silyl ether with the substrate. Silyl groups are particularly useful for this purpose because they can be installed and removed very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

7. A

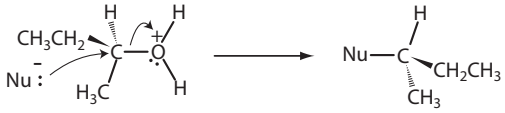
You will often see a hydroxyl group serving as the target of phosphoryl transfer in biochemistry. Because the hydroxyl group serves as the nucleophile in a phosphoryl transfer reaction, it is the same extracyclic oxygen on the anomeric carbon in phosphoribosyl pyrophospate after the reaction as had been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

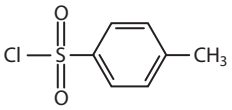


8. C

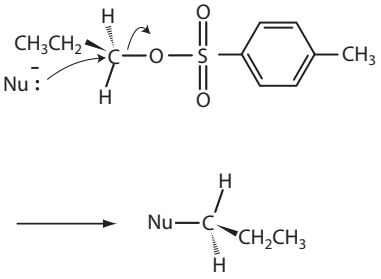
It is a very important thing about the hydroxyl group to understand that it is a *very poor leaving group*. One way to get a hydroxyl group to leave is by acid catalysis. This way it can leave as water.



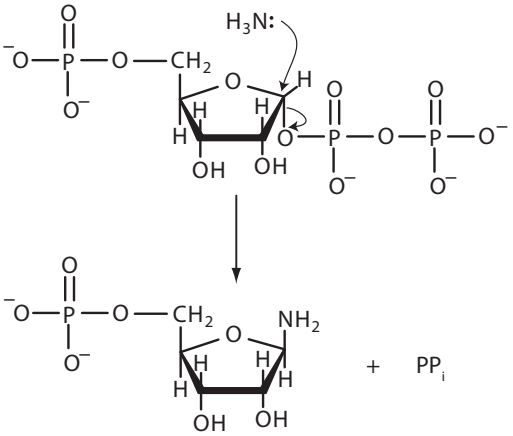
This is *p*-toluenesulfonyl chloride:



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.

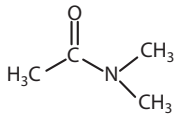


9. B

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

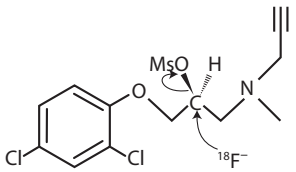
Dimethylacetamide (DMA) is a polar aprotic solvent. While having a high dielectric constant (polar), it does not possess any hydrogens bonded to electronegative elements, such as in hydroxyl or amine groups.



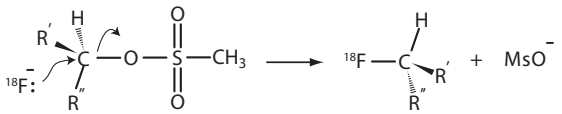
Polar aprotic solvents are the optimal type of solvent for SN2 substitution. Their dielectric property helps stabilize the charge separations of the transition state, but unlike a protic solvent, they don't carry out the hydrogen bonding that would cage and over-stabilize the nucleophile.

11. D

Steps 4 has SN2 substitution on a chiral center.

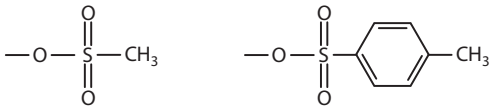


SN2 substitution leads to inversion of configuration. While Steps 1 and 2 are also SN2 substitution, inversion of configuration is only stereochemically dispositive with a chiral center.



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

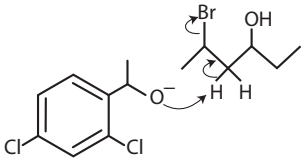
Sodium hydride (NaH) is is a very strong base (a superbase) capable of deprotonating even very weak Brønsted acids. NaH has utility in organic chemistry where typical substrates contain O-H, N-H, S-H bonds. The abstraction of the proton from 2,4-dichlorophenol in Step 1 of our synthesis converts the 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).