1) The pKₐ values of acetic acid and trifluoroacetic acid are 4.5 and 0.9 respectively. Based on this information, which anion, CH₃COO⁻ or CF₃COO⁻, is a better leaving group?

The lower the pKₐ, the better the acid (remember pKₐ = -log(K_a)). Therefore, since the pKₐ of trifluoroacetic acid is lower than that of acetic acid, I would say that trifluoroacetate anion is a better leaving group that acetate.

2) Draw the Newman projection formulas of the conformations leading to both cis and trans alkenes in the following reaction:

\[
\text{OTs} \quad \text{CH}_3\text{CH}_2\text{O}^-\text{Na}^+ \quad \text{ethanol} \quad \text{heat} \quad \text{CH}_3\text{CH}_2\text{CH}≡\text{CHCH}_3
\]

Point out which proton will be removed by the base and identify all the unfavorable interactions in the Newman projection. Use this information as your guide to predict which isomer is likely to predominate in the reaction. (N.b.: you need two Newman projection diagrams; one for the cis, and another one for the trans.)

Here are the two Newman projections:

The conformer leading to the trans alkene (the one on the right) has fewer unfavorably interactions, and therefore should be more preferred; therefore, the trans alkene should be the observed product.
3) Explain why optically active \((R)\) -2-iodopentane racemizes on standing in a solution of sodium iodide in acetone.

In words: the iodide ion (from the NaI) does an S\(_2\)N on the \((R)\)-2-iodopentane, making it the \((S)\) enantiomer. Statistically, this process goes on, with more \((R)\) reacting than \((S)\) until there is an equimolar mixture of R and S. At this point, for every R which goes to S, one S goes to R—you are now at a steady state which is also a racemic mixture.

In pictures:

Initially, there is more (much more) of the iodide on the left than on the right; with time, the amount on the left decreases and the amount on the right increases. When these are equal (or very nearly so), then for each forward reaction, there is a reverse reaction. Also notice that the iodide ion is, essentially, catalytic.

4) An optically pure nitrile, shown below, was required for a research project (not mine!). the student responsible for obtaining 10 g of this material was able to find only three-quarters of this amount; the rest had to be synthesized. Both \((R)\) and \((S)\) enantiomers of 2-bromobutane were available, so the student decided to perform the reaction involving \((R)\)-2-bromobutane and NaCN in DMF. The reaction proceeded as expected (that is, it went in a forward direction), and the proud student combined the original nitrile sample with 2.5 g of the newly synthesized material. Routine measure of \([\alpha]\) of the combined nitrile sample revealed that it was no longer optically pure. What went wrong? What was the optical purity of the sample? (This last part is a some harder question.)

Our student needs to get the \((R)\) enantiomer, so starting with the R-bromide was sort of foolish. His reaction is (clearly) S\(_2\)N2, so he should expect to get the \((S)\) enantiomer. In short, he picked the wrong enantiomer of the bromide with which to start.

Having mixed 2.5 g of the \((S)\) nitrile with 7.5 g (\(3/4\) of the needed amount of 10 g) of the \((R)\), he now has 5.0 g of pure R and 5.0 g of a racemic mixture. Our optical purity
can be assessed as follows: optical purity = \( \frac{[R] - [S]}{[R] + [S]} \). Doing so gives us \( \frac{5.0}{10.0} = 0.5 \) or 50%.

5) Each of the following reactions gives a substitution product. Identify the major product in each case and indicates whether the reaction is likely to proceed via a bimolecular (S\(_N\)2) or a unimolecular (S\(_N\)1) mechanism.

![Chemical structure](Image)

Mechanism is most likely an S\(_N\)2 reaction, giving as a major product:

![Product Structure]

no stereochemistry specified.

b)

![Chemical structure](Image)

A tertiary mesylate (similar to a tosylate)—hmm—seems to me to be (clearly) S\(_N\)1. Here’s the product:

![Product Structure]

Hmm. Another tertiary substrate, this one a bromide. Again, (clearly) an S\(_N\)1 reaction, with major product being:
Some stereochemistry to keep you on your toes! Secondary substrate, decent leaving group, polar solvent—sounds like ideal conditions for the $S_N2$ reaction. Here is the stereochemically correct product:

$$\text{CN}$$

Again, nice nucleophile, unhindered halide—$S_N2$ reaction.

$$\text{An } S_N2 \text{ reaction with somewhat different substrates than we’ve normally seen. The second compound (dimethylsulfate) is quite similar to methanesulfonyl chloride, a}$$
relative of \( p \)-toluenesulfonyl chloride. Related compounds do similar reactions. Here’s the product:

![Image of the product](image)

6) **Draw the expected product when sodium cyanide reacts with each of the following substrates. Pay attention to stereochemistry where appropriate.**

![Substrate a](image)

![Substrate b](image)

Okay. We might have done one or both of these in class. Both are \( S_N2 \) reactions, and both go nicely. Here are the products.

![Product a](image)

![Product b](image)

7) **Give the major elimination product derived from each of the following elimination reactions. Pay attention to stereochemistry where appropriate.**

![Elimination reaction a](image)
8) When cis-1-iodo-2-methylcyclohexane is treated with potassium tert-butoxide, the major product is 1-methylcyclohexene, a trisubstituted alkene. However, when the corresponding trans isomers is subjected to the same conditions, the reaction progresses at a slower rate and the major product is 3-methylcyclohexene, a disubstituted alkene. Explain these observations. You may provide the arrow formalism (a mechanism) if that helps your answer.

Whenever confront with problems similar to this one, it is a very good idea to draw more realistic looking 3-D structures (or at least get the cyclohexane in the chair conformation!) Doing so, we get:

Now we can start to examine the “why” of the question. We can see that in the cis case, the methyl is in the preferred equatorial position, and that the iodine and the hydrogen on the carbon with the methyl are pretty nearly anti-periplanar, which is the required arrangement (conformation) for a good E₂ reaction. This reaction also yields the favored, Saytzev’s product. Hence, a good, fast reaction.
In the cis case, the ring has to flip to give a good anti-periplanar arrangement for an H and the I; this flip also puts the methyl in the less preferred axial position. The ring flip is “slow” relatively speaking, so the reaction is slow. Here it is in pictures:

![Chemical structure](image)

Note that it is the **bold** hydrogen which is lost.

9) Provide effective syntheses of the following molecules from any suitable starting materials.

a) There are a couple of decent disconnects, shown below. I’ll provide syntheses from both.

![Chemical structure](image)
Here’s probably the easiest: