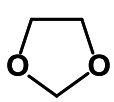
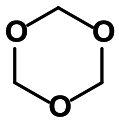
Mechanistic Assignment
CHEM 4000A – Medicinal Chemistry
Due at 12:00 noon on Friday, November 2, 2012

In the interest of posting this answer key in a timely fashion, there are no lone pairs drawn in the mechanisms. You were expected to include lone pairs (which take much less time to add when hand drawing the structures).

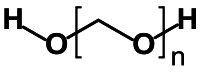
1. …



1,3-dioxolane



1,3,5-trioxane

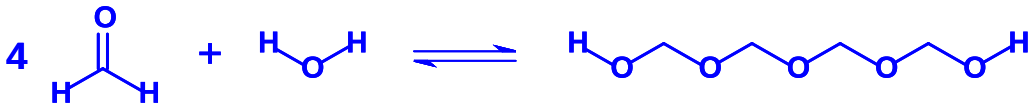


paraformaldehyde

(a) Paraformaldehyde can be used to generate very pure formaldehyde for use in some biological labs. Heating paraformaldehyde gives formaldehyde gas in an equilibrium process.

(i) Write a balanced chemical equation for the equilibrium between formaldehyde and paraformaldehyde. Instead of using the abbreviated form above, set n=4 and draw the whole molecule. 2 marks

(n is usually much larger than 4, but nobody wants to draw the whole molecule with n>>100!)



(ii) Why does this equilibrium favour paraformaldehyde at low temperatures but favour formaldehyde at high temperatures? 4 marks

Hint: You may need to go back to concepts from CHEM 2000 and/or CHEM 2500…

$$\Delta G = \Delta H - T\Delta S$$

In order for a reaction to be thermodynamically allowed, it must have a negative ΔG.

A reaction is enthalpy-favoured if ΔH is negative, and entropy-favoured if ΔS is positive.

If the forward reaction was favoured at all temperatures, it would be favoured by both entropy and enthalpy. Since (as written) the forward reaction is favoured at lower temperatures and the reverse reaction is favoured at higher temperatures, the forward reaction must be favoured by enthalpy (which dominates when T is small) and the reverse reaction must be favoured by entropy (which dominates when T is large).

Looking at the chemical equation, it makes sense that the forward reaction would be enthalpy-favoured since π bonds are broken to form σ bonds. Heat is released when bonds are formed and, since σ bonds are typically lower in energy than π bonds, one would expect heat to be released when four π bonds are broken and four σ bonds are formed.*

It also makes sense that the reverse reaction would be entropy-favoured since formaldehyde is a gas under standard conditions. So, the reverse reaction makes five small molecules, four of which can enter the gas phase, from one large molecule (which cannot enter the gas phase). Reactions generating more moles of gas than they start with are usually entropy-favoured.

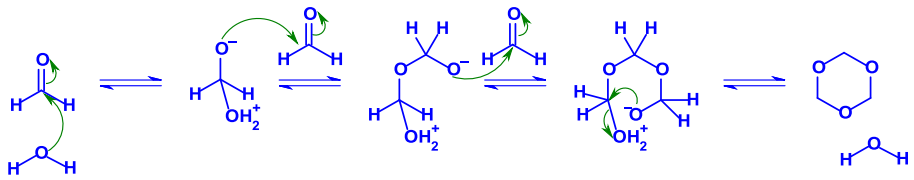
*One student noted that C=O bonds are unusually strong, implying that C-O π bonds are unusually strong. While this is true (and much more heat would have been released if we were breaking C-C π bonds and forming C-C σ bonds), it does not negate the point made here. C=O bond strengths listed in bond energy tables are usually for CO_2 which contains extra-specially strong C=O bonds because the C-O bond order in CO_2 is actually a little higher than 2 (see MO diagram for CO_2 in CHEM 2000 notes, or build it yourself in HyperChem to see the extra contribution to each "double" bond from the other pi system.)

(b) Chemists tend to prefer 1,3,5-trioxane over paraformaldehyde for practical reasons. As a polymer, paraformaldehyde is fairly insoluble in most solvents whereas 1,3,5-trioxane dissolves in a variety of common organic solvents. Addition of a catalytic amount of acid to the solution is usually necessary.

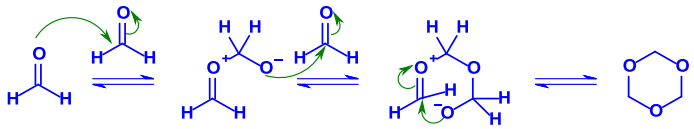
(i) Suggest a reasonable mechanism for the formation of 1,3,5-trioxane from formaldehyde.

You may assume that water is present. 3 marks

Many students made this mechanism much more complicated than it needed to be. I'm showing the two versions that seem most reasonable to me.



or



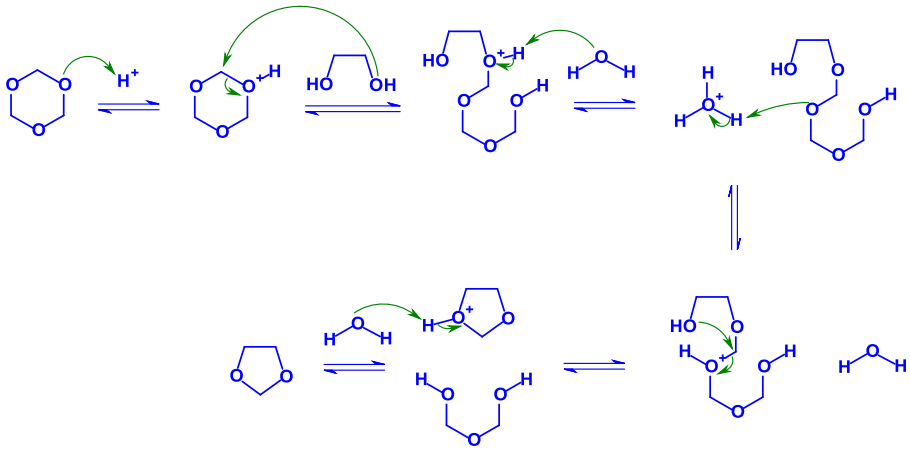
The most common mistake, by far, was protonating ROH in the presence of RO^-.

RO^- is substantially more basic than ROH due to the negative charge on the oxygen atom.

(ii) Suggest a reasonable mechanism for the formation of 1,3-dioxolane from 1,3,5-trioxane and 1,2-ethanediol in the presence of catalytic acid. 4 marks

You may use H^+ as a generic acid. The solvent is 1,2-ethanediol.

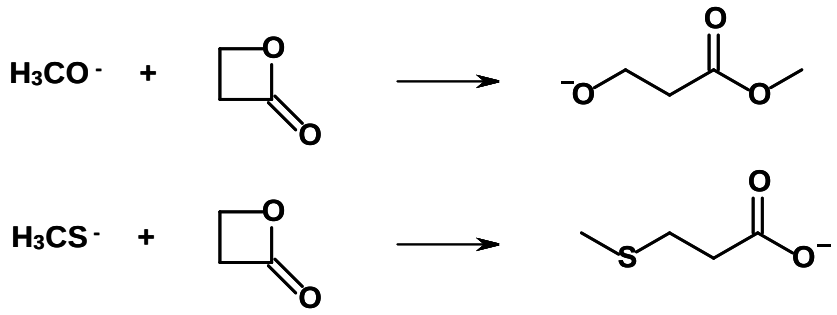
You may not, under any circumstances, use hydroxide ions (or other RO^-) in a mechanism for a reaction in acid. They are strong bases and would be protonated instantly by the acid. They are also poor leaving groups and O requires protonation to make a better leaving group in acidic reaction mechanisms (which rarely involve the very strong nucleophiles required to displace weak leaving groups since those very strong nucleophiles tend to be bases too).



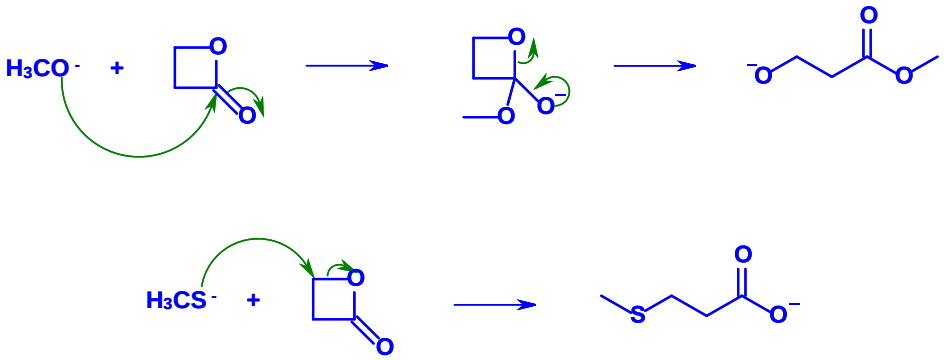
There was no need to fully degrade the 1,3,5-trioxane into formaldehyde pieces before using one to make the 1,3-dioxolane.

You must use water to deprotonate the second intermediate (as drawn) then H_3O^+ (or more H^+) to protonate the other oxygen atom. Direct transfer of H^+ would require formation of a square transition state, so the second O "cannot reach" the H on the O^+.

2. Suggest a reasonable mechanism for each of the two reactions below, and explain the key difference(s) between them.



The mechanisms were generally well done. The explanations of why RS^- is softer than RO^- were also good; however, many did not clearly explain why one electrophilic site would be softer than the other.



2 marks

1 mark

In both reactions, ring strain is relieved by attack of a nucleophile leading to an acyclic product.

The primary difference between the two reactions is the electrophilic site attacked by the nucleophile.

The best explanation for why RS^- attacks a different electrophilic site than RO^- is based on hard-soft acid-base theory (HSAB). RS^- is a softer nucleophile than RO^- so it attacks the softer electrophilic site. RO^- is a harder nucleophile so it attacks the harder electrophilic site.

RS^- is a softer nucleophile than RO^- because there is less charge density on the sulfur atom. Both S and O have a charge of -1 that is not delocalized onto any other atom; however, S is a larger atom than O so the charge density on S is lower, making it a softer nucleophile.

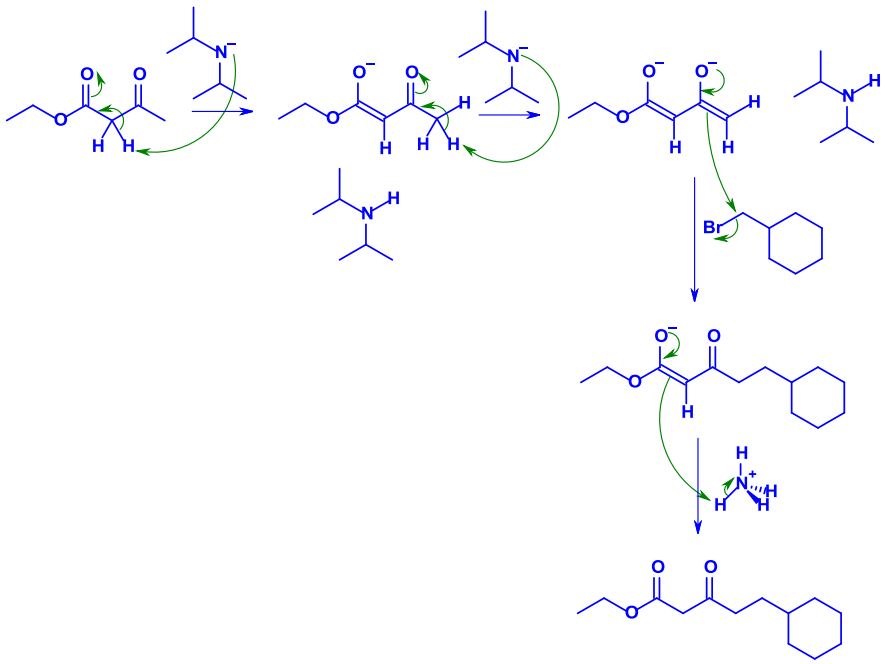
The electrophilic site attacked by RS^- is the softer site because it has a less positive carbon atom (compared to the carbonyl carbon). It has one polar C-O bond, making it slightly positive and therefore electrophilic. The carbonyl carbon, on the other hand has a polar C-O bond and a polar C=O bond, making the that carbon more positive. Since the two carbon atoms are the same size, the charge density on the carbonyl carbon is higher, making it harder.

4 marks

3. Consider the following sequence of reactions:

…

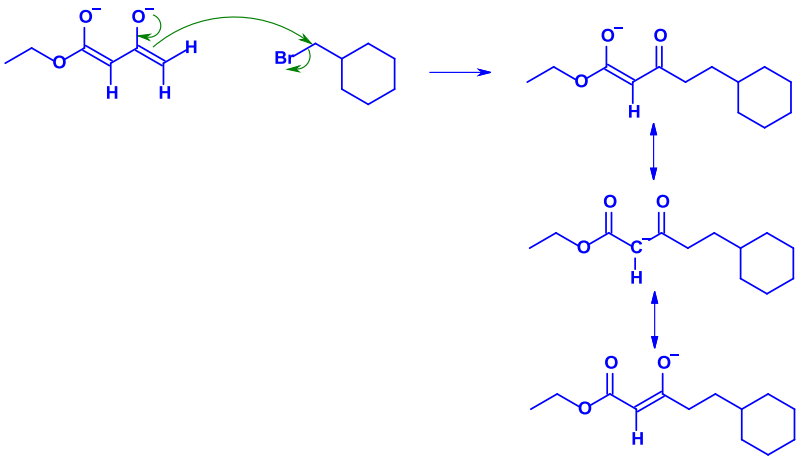
(a) (i) Suggest a reasonable mechanism for step #1. Clearly indicate when experimental conditions change (i.e. when a new reagent is added). 4 marks



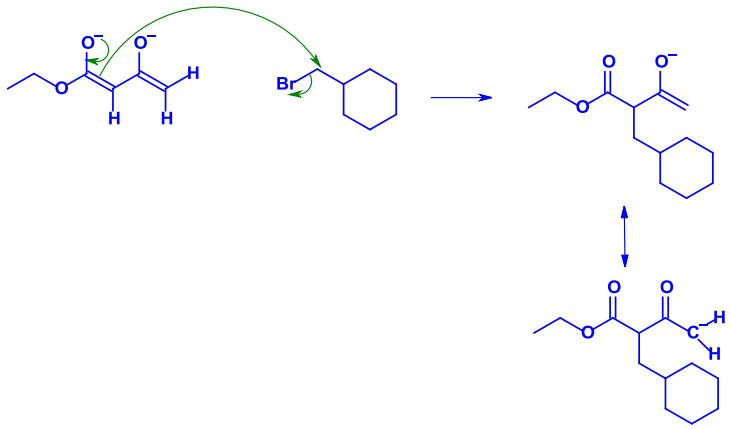
(ii) With reference to your mechanism, explain why the β-ketoester reacts at the terminal carbon instead of the carbon between the two carbonyl groups. 3 marks

Anytime a molecule is deprotonated more than once, the last anion formed will be the least stable and therefore the most reactive. As shown in the mechanism above, the most acidic hydrogen (pK_a ~11) is removed first. The terminal methyl group is then deprotonated as that negative charge can also be delocalize into the pi system.*

It is probably easiest to see why the terminal carbanion (second one formed) is more reactive by looking at the structures of the potential products using each carbanion as the nucleophile. The product formed by reaction of the terminal carbanion is more stable. The remaining negative charge is delocalized over three atoms (two O and one C):



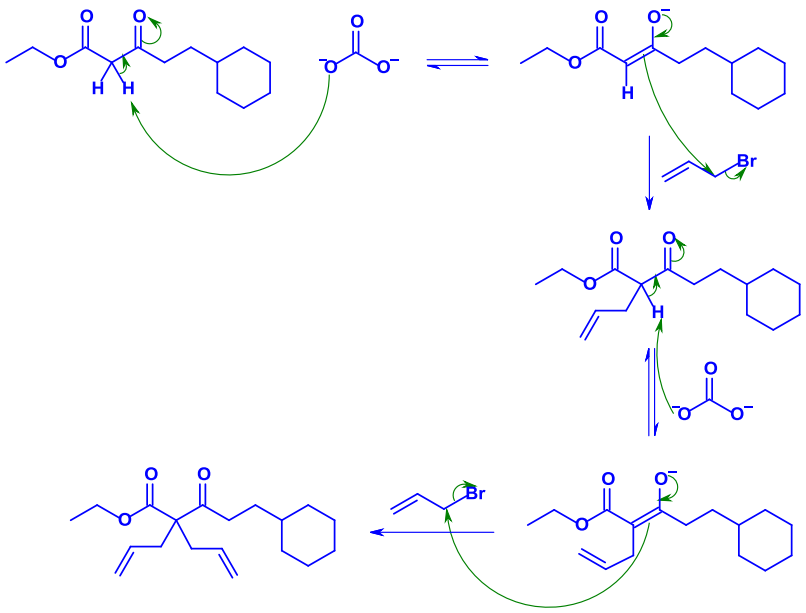
The product formed by reaction at the central carbanion also has a negative charge and it is only delocalized over two atoms (one O and one C):



Thus the product formed when the central carbanion is used as the nucleophile is less stable than the product formed when the terminal carbanion is used as the nucleophile.

If it were the only acidic proton in the molecule, a methyl ketone proton would have pK_a ~20. This value is raised when an anion is being deprotonated (since it is more difficult to make a dianion than the equivalent monoanion). That's why such a strong base (LDA – pK_a of conjugate acid ~35) is required to remove the second proton.

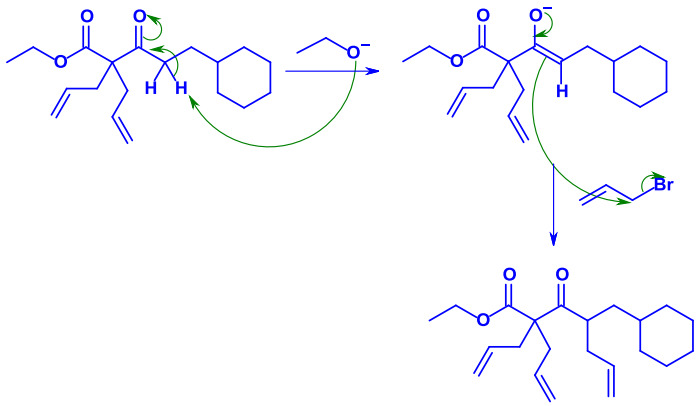
(b) (i) Suggest a reasonable mechanism for step #2. 4 marks



(ii) Why would K_2CO_3 have been used instead of NaOEt? Important factors to consider include acidity of the β-ketoester, strength of the bases and possible side reactions. 4 marks

The pK_a for the methylene (CH_2) group between the two carbonyl groups is ~11. HCO_3^- (the conjugate acid of CO_3^{2-}) has a pK_a value of 10. So, carbonate is a strong enough base to deprotonate a significant fraction of the dicarbonyl compound (~10% at any moment in time).

NaOEt (effectively, EtO^-) is also a strong enough base to deprotonate the doubly activated methylene protons since its conjugate acid, EtOH, has pK_a ~15. Unlike carbonate, though, EtO^- is a nucleophilic base and might react with the allyl bromide to give 3-ethoxypropene (aka allyl ethyl ether). Also, if the stoichiometry was not carefully controlled, it might react with some of the intended final product, deprotonating on the other side of the ketone, generating another carbanion which could react with more allyl bromide:



If there was a sufficient excess of reagents, this could even happen again…

(c) What is a "ring closing metathesis" reaction? Your answer should address the types of reactants involved, whether each is used in stoichiometric or catalytic amounts and a reasonable mechanism for step #3. 4 marks for mechanism; 2 marks for further info. about ring closing metathesis

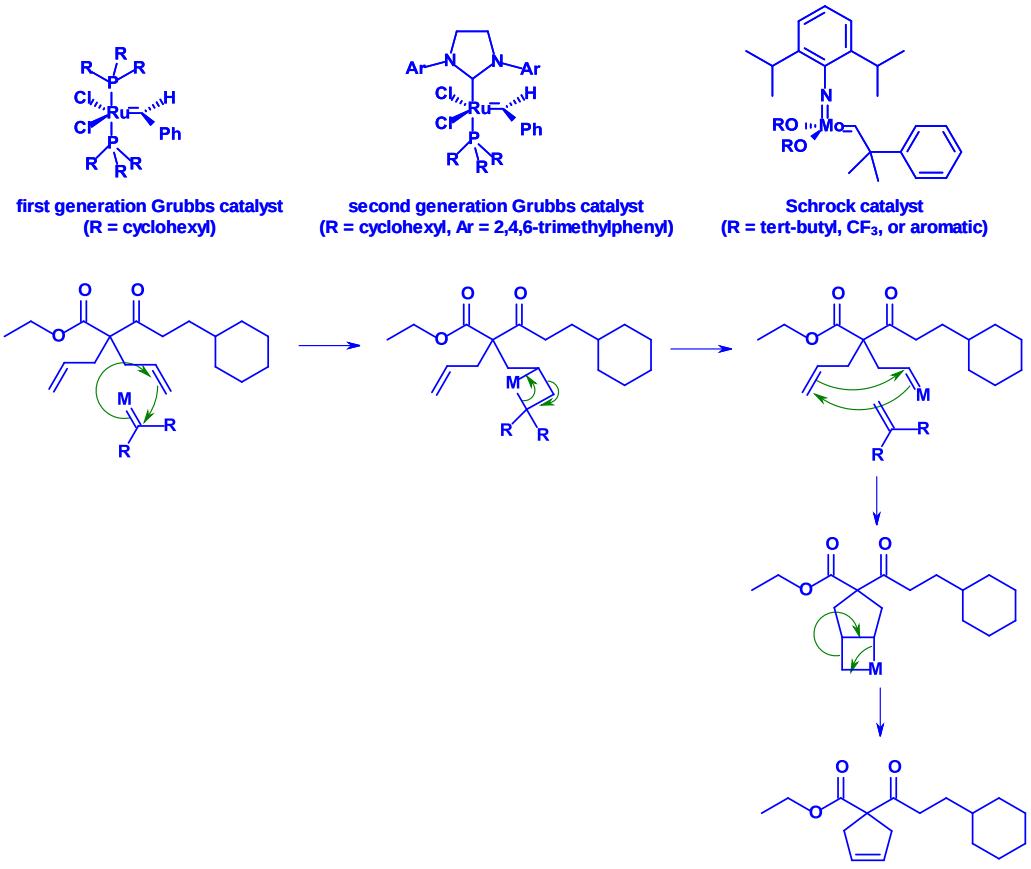
Metathesis reactions are important enough that they merited a Nobel Prize.

A ring closing metathesis is an olefin metathesis reaction in which the final product is a cycloalkene.

In a metathesis reaction, two alkenes are reacted in such a way that half of each alkene becomes attached to half of the other alkene. i.e. A=B + C=D $\rightarrow$ A=D + C=B

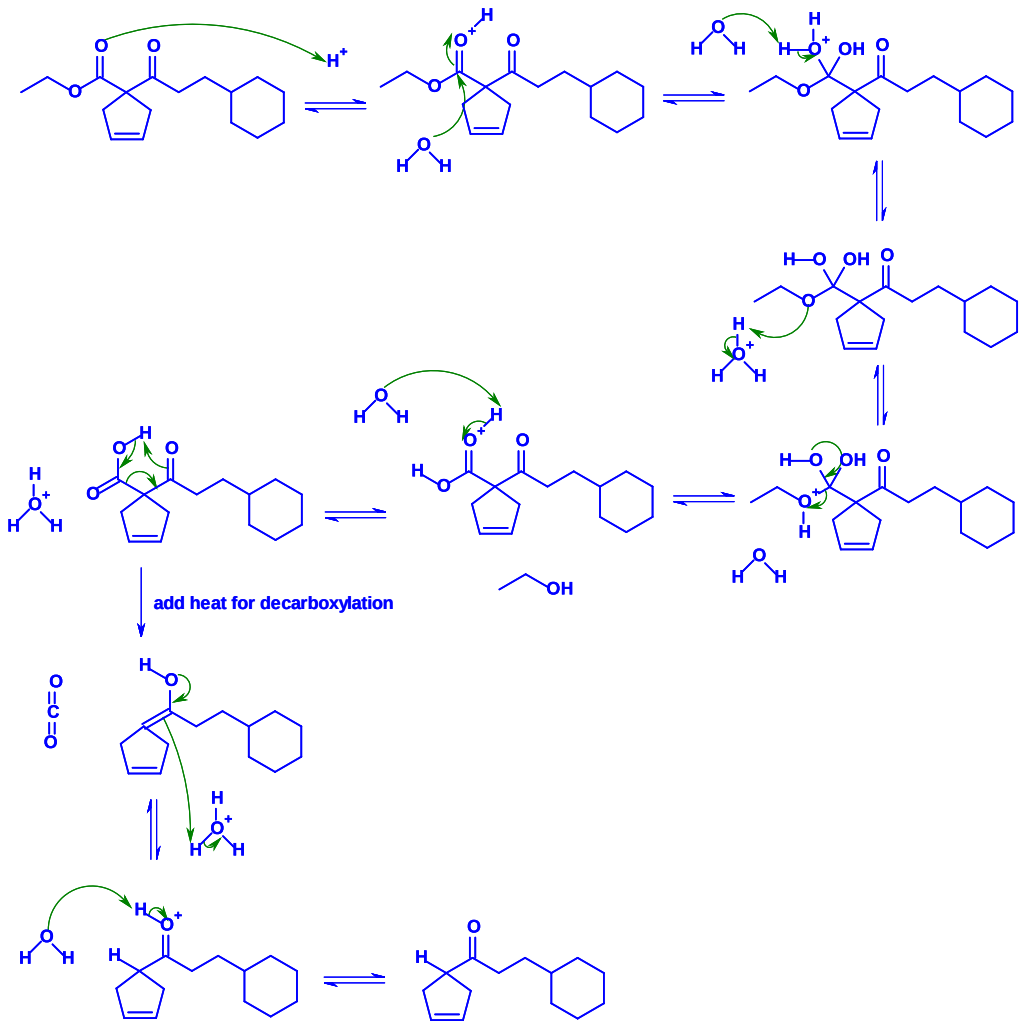
In the case of a ring closing metathesis, both alkenes are part of the same molecule. Thus, a cycloalkene is produced as one of the two products. The other is usually ethene (though it can be other alkenes – usually symmetric and usually small so that they are easy to separate from the desired product).

To perform a metathesis reaction, a catalyst is required. The majority of metathesis catalysts contain either Ru or Mo and, in either case, the metal has a double bond to carbon (in addition to other ligands). Grubbs catalysts contain Ru while Schrock catalysts contain Mo. Sample catalyst structures are shown below. In the mechanism that follows, the catalyst will be abbreviated as $M{=}CR_2$.



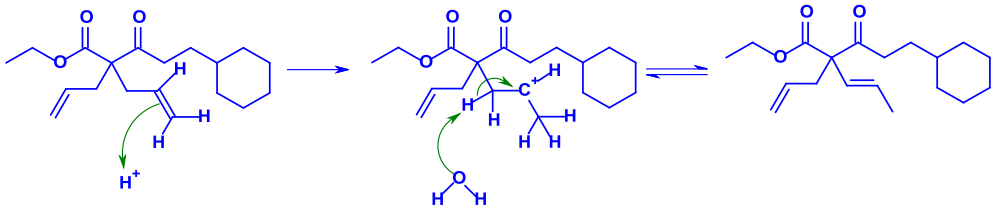
(d) (i) Suggest a reasonable mechanism for step #4. 6 marks

You may abbreviate non-reacting parts of the molecule as R, R', etc.



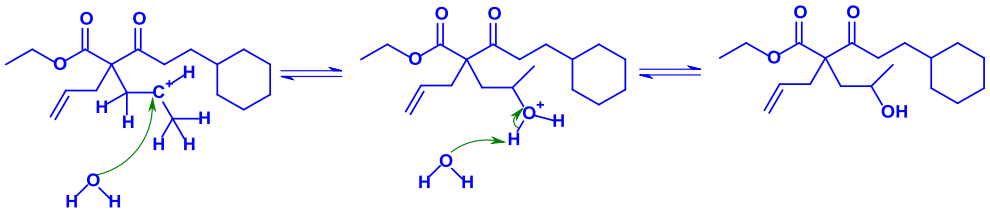
(ii) Why would steps #3 and #4 have been done in this order rather than in reverse? 3 marks

Alkenes can act as bases, and a terminal alkene in the intermediate could be protonated to give a secondary carbocation. This would likely be followed by elimination; however, the double bond would migrate away from the less stable terminal monosubstituted position to a more stable disubstituted position:



This could happen to both terminal alkenes.

It is also plausible that the carbocation could react with water in an S_N1 reaction, giving the secondary alcohol(s):



Elimination could be used to convert the secondary alcohol back into an alkene but, again, the disubstituted alkene (shown above) would be formed.

With the alkene(s) no longer terminal, the product of ring closing metathesis would no longer be a cyclopentene. It would be either a cyclobutene or a cyclopropene.