Appendix 1

pK_a Values of Protons Associated with Common Functional Groups

While this book teaches that organic chemistry can be learned without relying upon memorization of a multitude of chemical reactions, familiarity with pK_a values associated with various functional groups is essential. The pK_a values listed below provide a general calibration of the acidities of protons associated with common functional groups. In advancing through organic chemistry, accurate recollection of these values is indispensable.

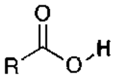
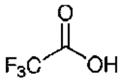
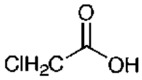
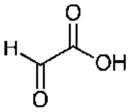
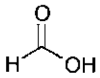
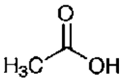
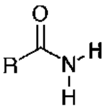
Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy

Common Protic Acids

H-F Hydrofluoric Acid	**3.18**	H-I Hydroiodic Acid	**−10**
H-Cl Hydrochloric Acid	**−2.2**	H-CN Hydrocyanic Acid	**9.3**
H-Br Hydrobromic Acid	**−4.7**	$H\text{-}N_3$ Hydrazoic Acid	**4.6**

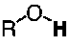
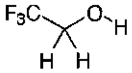
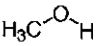
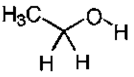
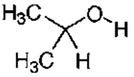
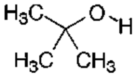
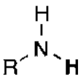
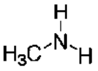
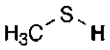
Neutral Functional Groups

Carboxylic Acids and Amides

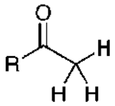
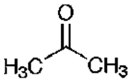
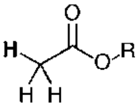
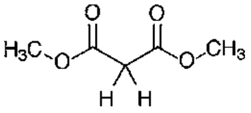
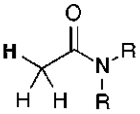
 Carboxylic Acids	**4–6**	 Trifluoroacetic Acid	**0.30**
		 Chloroacetic Acid	**2.85**
		 Glyoxylic Acid	**3.18**
		 Formic Acid	**3.75**
		 Acetic Acid	**4.75**
 Amides	**15–17**		

Neutral Functional Groups—Continued

Alcohols, Amines, and Thiols

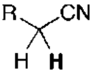
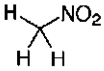
 Alcohols	15–19	 2,2,2-Trifluoroethanol	11–12
		 Methanol	15
		 Ethanol	15–16
		 2-Propanol	16–17
		 2-Methyl-2-propanol	18–19
 Amines	33–38	$H_2N{-}H$ Ammonia	35
		 Methylamine	35
	 Methanethiol	10.4	

Aldehydes, Ketones, Esters, and Amides

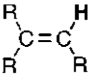
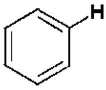
 Aldehydes and Ketones	20–25	 Acetone	20
 Esters	25–30	 Dimethyl Malonate	13
 Second Amides	30–35		

Neutral Functional Groups—Continued

Nitriles and Nitro Compounds

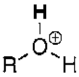
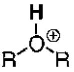
 Nitriles	20–25	H_3C-CN Acetonitrile	25
		 Nitromethane	10–15

Alkanes, Alkenes, and Alkynes

H_3C-H Alkanes	50–75	$R-C\equiv C-H$ Alkynes	25
 Alkenes	35–40	 Benzene	40–45

Protonated Functional Groups

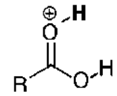
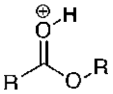
Alcohols and Ethers

 Alcohols	−2.2	 Ethers	−2.2

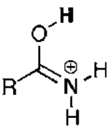
Amines

$(CH_3CH_2)_3\overset{\oplus}{N}-H$ Amines	10

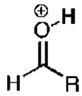
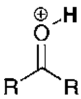
Carboxylic Acids and Esters

 Carboxylic Acids	−6	 Esters	−6

Amides and Nitriles

 Amides	0	$H_3C-C\equiv\overset{\oplus}{N}-H$ Nitriles	−10

Aldehydes and Ketones

 Aldehydes	−7 to −9	 Ketones	−7 to −9

Appendix 2

Answers and Explanations to Problems

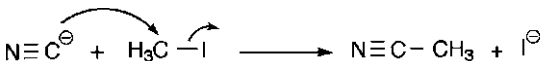
CHAPTER 1 SOLUTIONS

1. *Use arrow pushing to explain the following reactions.*

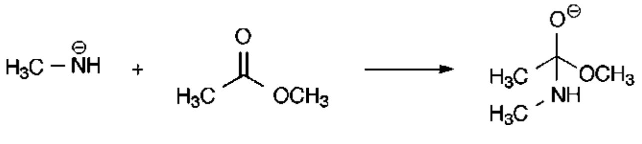
When drawing arrows to illustrate movement of electrons, it is important to remember that electrons form the bonds that join atoms. The following represent heterolytic-type reaction mechanisms:

a. $N{\equiv}C^{\ominus} + H_3C{-}I \longrightarrow N{\equiv}C{-}CH_3 + I^{\ominus}$

This is an example of an S_N2 reaction mechanism converting an alkyl iodide (iodomethane) to an alkyl nitrile (acetonitrile). Arrow pushing is illustrated below:



b.



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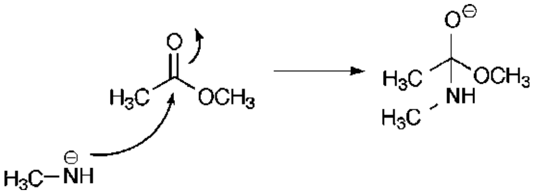
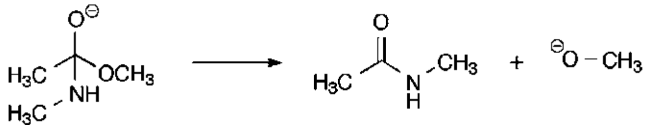
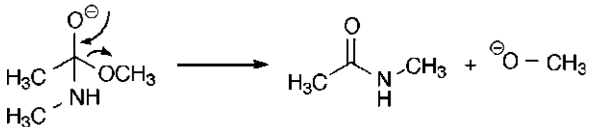
This is an example of the first step of an addition–elimination reaction mechanism converting an ester (methyl acetate) to an amide (*N*-methylacetamide). For clarity, the anion was repositioned in the scheme. Arrow pushing is illustrated below:



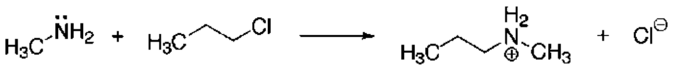
c.



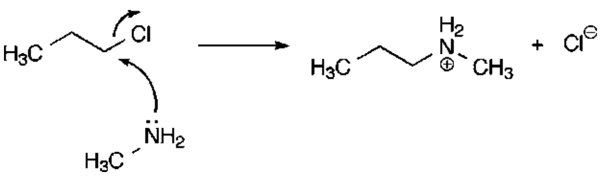
This is an example of the second step of an addition–elimination reaction mechanism converting an ester (methyl acetate) to an amide (*N*-methylacetamide). Arrow pushing is illustrated below:



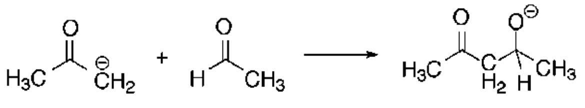
d.



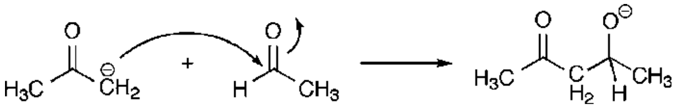
This is an example of an S_N2 reaction mechanism converting an alkyl chloride (chloropropane) to an ammonium salt (*N*-methyl, *N*-propylammonium chloride). For clarity, the amine was repositioned in the scheme. Arrow pushing is illustrated below:



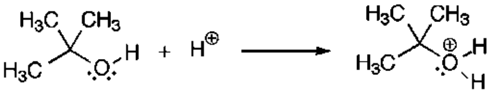
e.



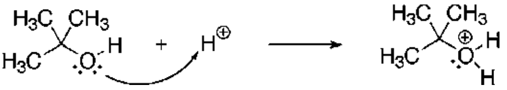
This is an example of an aldol condensation between an acetone anion and acetaldehyde. Note the mechanism proceeds through addition of an anion to an aldehyde carbonyl. Arrow pushing is illustrated below:



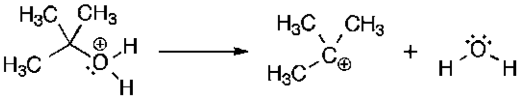
f.



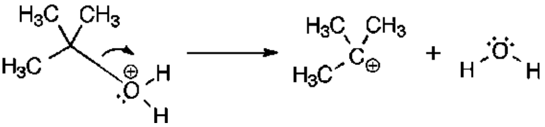
This is an example of the first step in the acid-mediated solvolysis of a tertiary alcohol. Note that protonation of the alcohol occurs under strongly acidic conditions with electrons moving toward the positive charge residing on the proton. Arrow pushing is illustrated below:



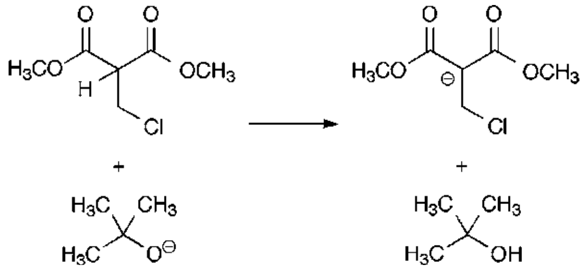
g.



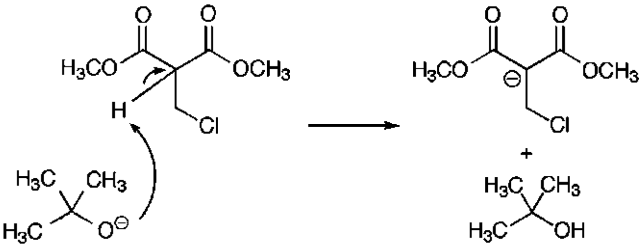
This is an example of the second step in the acid-mediated solvolysis of a tertiary alcohol. Note that the protonated alcohol separates as water and leaves the positive charge on the carbon atom. For clarity, the bond was lengthened to allow space for the arrow. Note that the electrons in the bond move toward the positive charge residing on the oxygen. Arrow pushing is illustrated below:



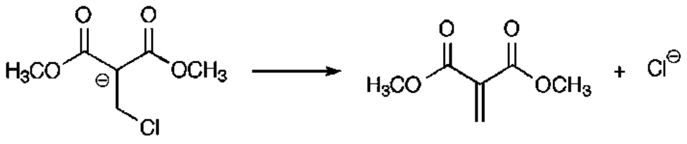
h.



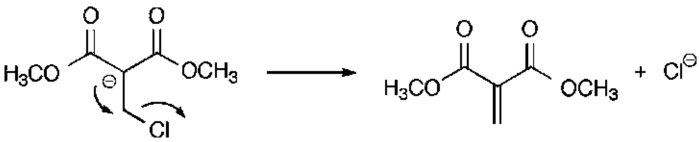
This is an example of the first step of an E2 (bimolecular elimination) reaction mechanism. Note the base-mediated deprotonation of the diester converting the *tert*-butoxide anion to *tert*-butanol. For clarity, the anion was repositioned and the bond was lengthened. Arrow pushing is illustrated below:



i.



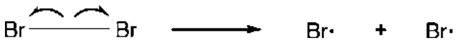
This is an example of the second step of an E2 (bimolecular elimination) reaction mechanism. Note the displacement of the chloride anion is the result of an anion present on an adjacent carbon atom. Arrow pushing is illustrated below:



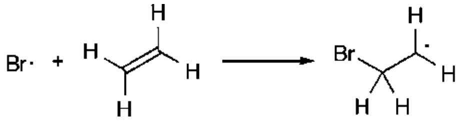
The following represent reaction mechanisms involving free radicals:

j. $\mathrm{Br{-}Br} \longrightarrow \mathrm{Br}\cdot + \mathrm{Br}\cdot$

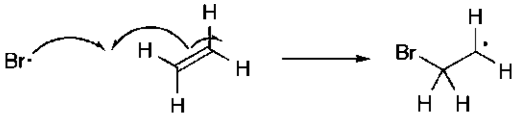
This is an example of the homolytic cleavage of a bromine molecule to form two bromide radicals. Note the use of single-barbed arrows to describe radical-based mechanisms resulting in the movement of single electrons. For clarity, the bond is elongated. Arrow pushing is illustrated below:



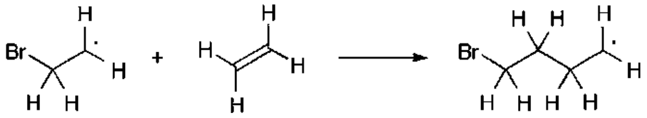
k.



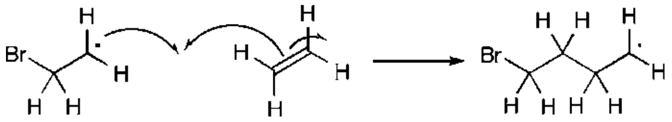
This is an example of the addition of a bromide radical to an olefin. Note that a single-barbed arrow is used for each electron that is moving. Arrow pushing is illustrated below:



l.

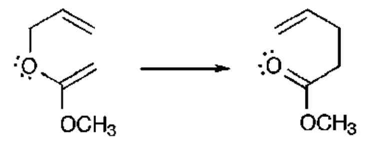


This is an example of a step in the free-radical-mediated polymerization of ethylene, forming polyethylene. As in the previous example, note that a single-barbed arrow is used for each electron that is moving. Arrow pushing is illustrated below:

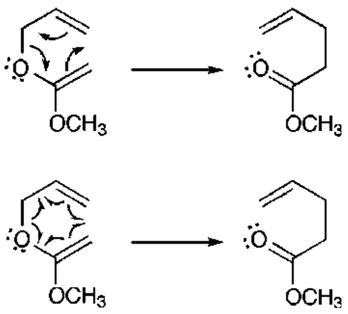


The following represents a concerted reaction mechanism:

m.

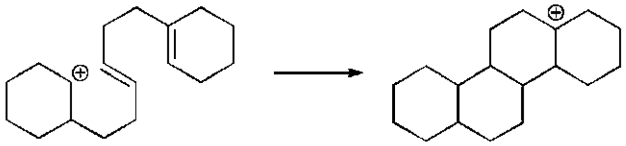


This is an example of a Claisen rearrangement and occurs through a concerted reaction mechanism. As illustrated, concerted mechanisms can be described either by movement of electron pairs or by movement of single electrons. However, these mechanisms are generally represented by movement of electron pairs using double-barbed arrows as is done for heterolytic reaction mechanisms. Although, mechanistically, the movement of electron pairs is preferred over the movement of single electrons, both processes are illustrated below using arrow pushing:

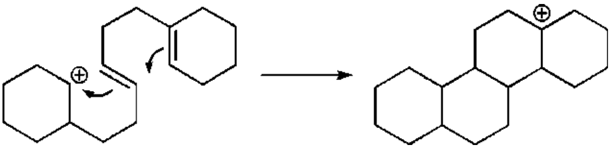


The following represents a heterolytic-type reaction mechanism:

n.

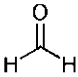


This is an example of a cation–π cyclization. Note that unlike the previously described heterolytic reaction mechanisms, this reaction is influenced by a positive charge. Also, please note that this reaction shares some characteristics with concerted mechanisms in that formation of the new bonds occurs almost simultaneously. Arrow pushing is illustrated below:

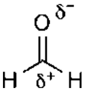


2. *Place the partial charges on the following molecules.*

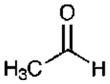
a.



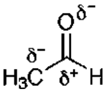
Carbonyls are polarized such that a partial negative charge resides on the oxygen and a partial positive charge resides on the carbon.



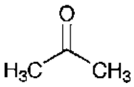
b.



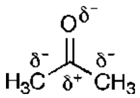
Because of the polarity of the carbonyl, adjacent groups are also polarized. In general, where a partial positive charge rests, an adjacent atom will bear a partial negative charge.



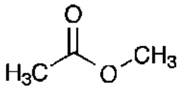
c.



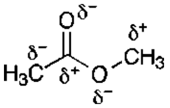
Because of the polarity of the carbonyl, adjacent groups are also polarized. In general, where a partial positive charge rests, an adjacent atom will bear a partial negative charge. This can occur on more than one adjacent atom.



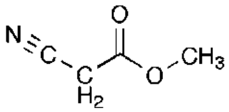
d.



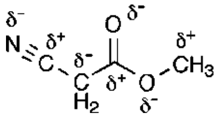
Because of the polarity of the carbonyl, adjacent groups are also polarized. In general, where a partial positive charge rests, an adjacent atom will bear a partial negative charge. This can occur on more than one adjacent atom or heteroatom.



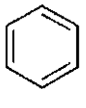
e.



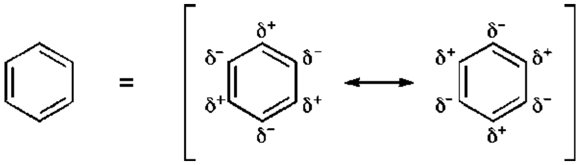
Nitriles, like carbonyls, are polarized with the nitrogen bearing a partial negative charge and the carbon possessing a partial positive charge.



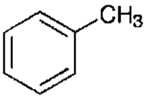
f.



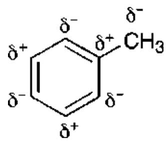
Benzene has no localized positive or negative charges because of its symmetry. The two illustrated resonance forms are equivalent, rendering benzene a nonpolar molecule.



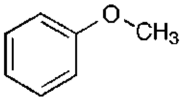
g.



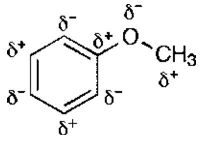
As will be discussed in Chapter 2, methyl groups are electron donating. This is not due to any defined positive charges on the carbon atom and is more the result of hyperconjugation. Hyperconjugation, in this case, relates to the ability of the carbon–hydrogen σ bonds of the methyl group to donate electrons into the conjugated system of benzene. While this effect will be discussed in more detail later, let us, for now, define methyl groups as possessing a formal partial negative charge. This resulting negative charge thus polarizes each double bond in the ring.



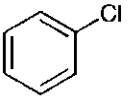
h.



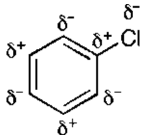
As with the previous example, groups possessing partial negative charge characteristics donate electrons into conjugated systems and polarize the double bonds. This effect is generally noted with heteroatoms such as oxygen. Also, while in the previous example a methyl group was argued to possess a partial negative charge, the partial positive charge illustrated here is due to the overriding partial negative characteristics of the oxygen atom.



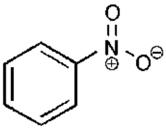
i.



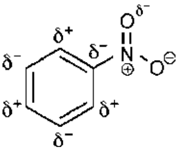
As with the previous example, heteroatoms such as chlorine possess partial negative charge characteristics and donate electrons into conjugated systems polarizing the double bonds.



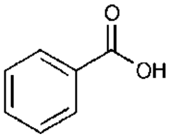
j.



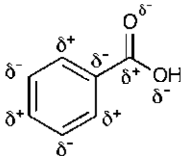
As with groups possessing negative charge characteristics, when a positive charge is present on an atom connected to a conjugated system, the double bonds are polarized. This polarization is opposite of that observed for negatively charged groups.



k.

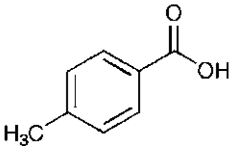


As with groups possessing negative charge characteristics, when a partial positive charge is present on an atom connected to a conjugated system, the double bonds are polarized. This polarization is opposite that observed for negatively charged groups.

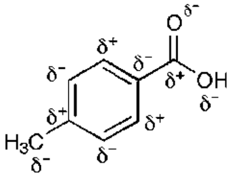


Please note for Problems 2l through 2r: When multiple groups are present on conjugated systems, their charged characteristics can work together or oppose each other depending on where they are placed relative to each other. The following problems address this point:

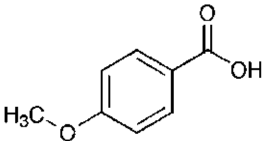
l.



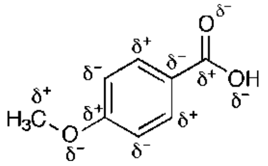
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *para* position. This is the same position where an electron-donating methyl group is placed. *Consider what impact the methyl group has on the acidity of the carboxylic acid.*



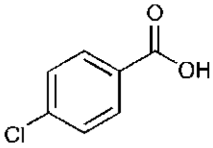
m.



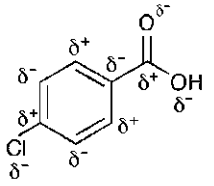
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *para* position. This is the same position where an electron-donating methoxy group is placed. Also, while in a previous example a methyl group was argued to possess a partial negative charge, the partial positive charge illustrated here is due to the overriding partial negative characteristics of the oxygen atom. *Consider what impact the methoxy group has on the acidity of the carboxylic acid.*



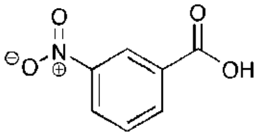
n.



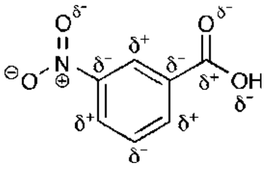
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *para* position. This is the same position where an electron-donating chloride is placed. *Consider what impact the chloro group has on the acidity of the carboxylic acid.*



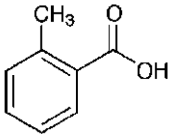
o.



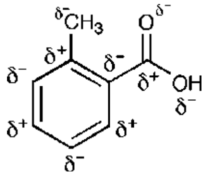
In this case, the carboxylic acid being electron withdrawing induces a partial negative charge at the *meta* position. This is the same position where an electron-withdrawing nitro group is placed. *Consider what impact the nitro group has on the acidity of the carboxylic acid.*



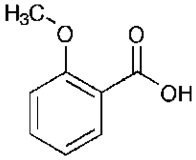
p.



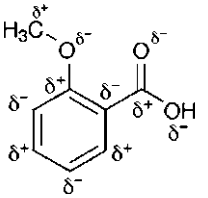
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *ortho* position. This is the same position where an electron-donating methyl group is placed. *Consider what impact the methyl group has on the acidity of the carboxylic acid.*



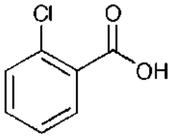
q.



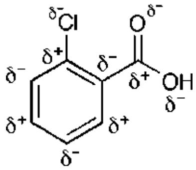
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *ortho* position. This is the same position where an electron-donating methoxy group is placed. Also, while in a previous example a methyl group was argued to possess a partial negative charge, the partial positive charge illustrated here is due to the overriding partial negative characteristics of the oxygen atom. *Consider what impact the methoxy group has on the acidity of the carboxylic acid.*



r.



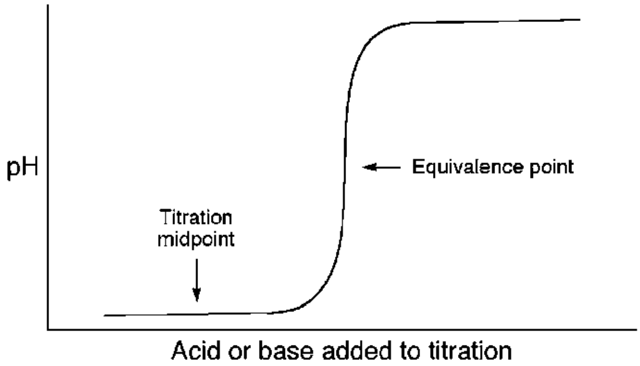
In this case, the carboxylic acid being electron withdrawing induces a partial positive charge at the *ortho* position. This is the same position where an electron-donating chloride is placed. *Consider what impact the chloro group has on the acidity of the carboxylic acid.*



CHAPTER 2 SOLUTIONS

1. *Explain how the Henderson–Hesselbach equation can be used, in conjunction with a titration curve, to determine a p*K_a*.*

When the progression of an acid–base titration is graphed as a function of pH vs the volume of acid or base added, the curve will appear as shown below. If we recall, from general chemistry coursework, that the steepest point on the curve represents the equivalence point of the titration (the point where the amount of acid and base are equal), we can locate the point on the curve that represents the midpoint of the titration. This point is found at half the concentration of base added to acid (or acid added to base) to reach the equivalence point. Once we have done this, we recall the Henderson–Hesselbach equation (Fig. 2.8)—specifically, the term dealing with the concentrations of the ionic and the neutral species. Realizing that at the midpoint of the titration, these concentrations are equal, the logarithmic term in the Henderson–Hesselbach equation reduces to log(1), which is equal to zero. Therefore, the equation reduces to $pK_a = pH$ at the midpoint of the titration.

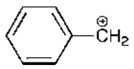


2. *What is the pH of a solution of acetic acid (p*$K_a = 4.75$*) that has been titrated with* $\frac{1}{4}$ *an equivalent of NaOH?*

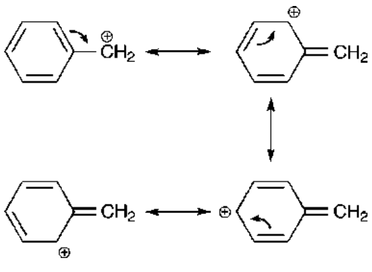
When acetic acid is titrated with $\frac{1}{4}$ an equivalent of base, we realize that the term $\log\{[A^-]/[HA]\}$ becomes $\log(\frac{1}{3})$ because one part out of four parts of acetic acid has been deprotonated. This leaves three parts acid to one part conjugate base. Filling in this value and that of the pK_a of acetic acid into the Henderson–Hesselbach equation (Fig. 2.8), solving for pH gives us a value of 4.27 as our answer.

3. *Draw the resonance structures of the following charged molecules:*

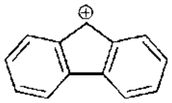
a.



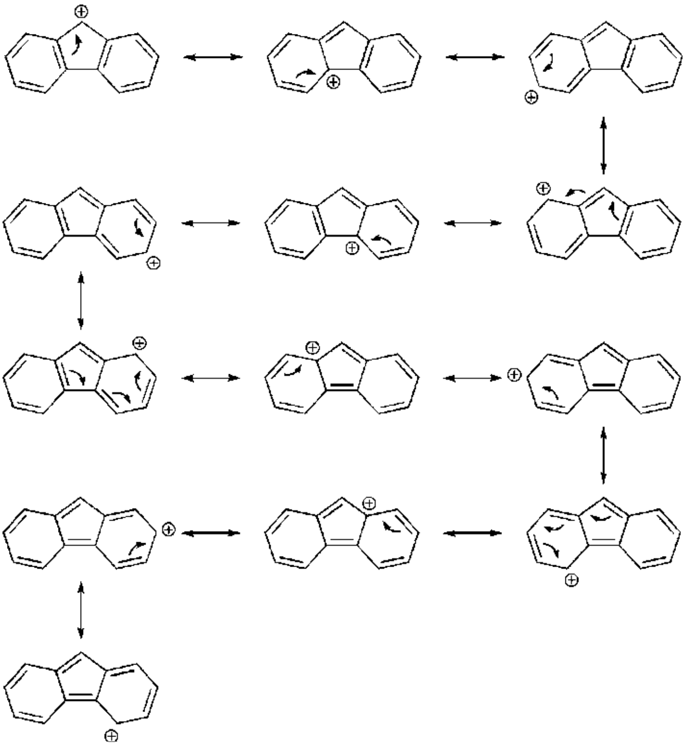
The following represent the resonance forms of the benzyl cation:



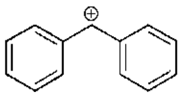
b.



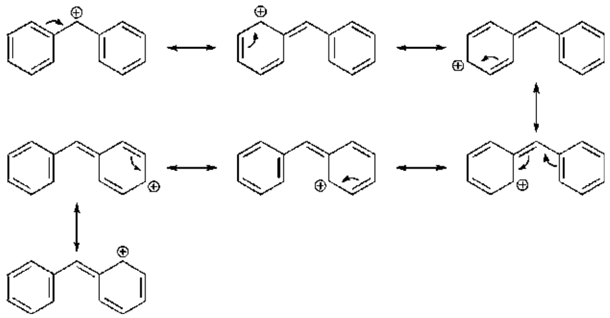
The following represent the resonance forms of the fluorenyl cation:



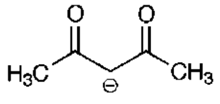
c.



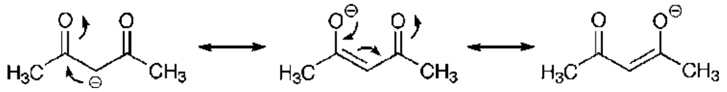
The following represent the resonance forms of the diphenylmethyl cation:



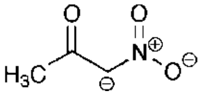
d.



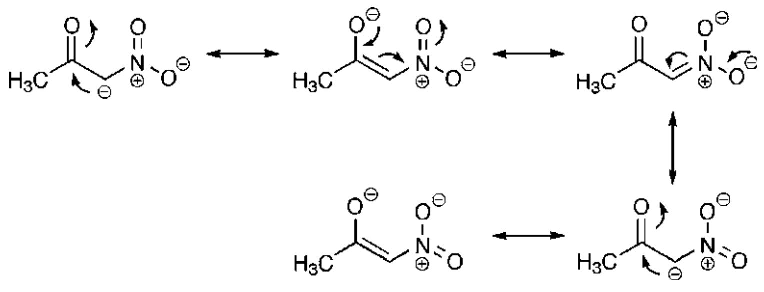
The following represent the resonance forms of the acetylacetone anion:



e.

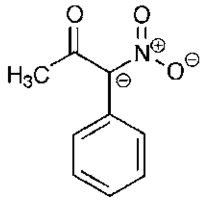


The following represent the resonance forms of the nitroacetone anion:

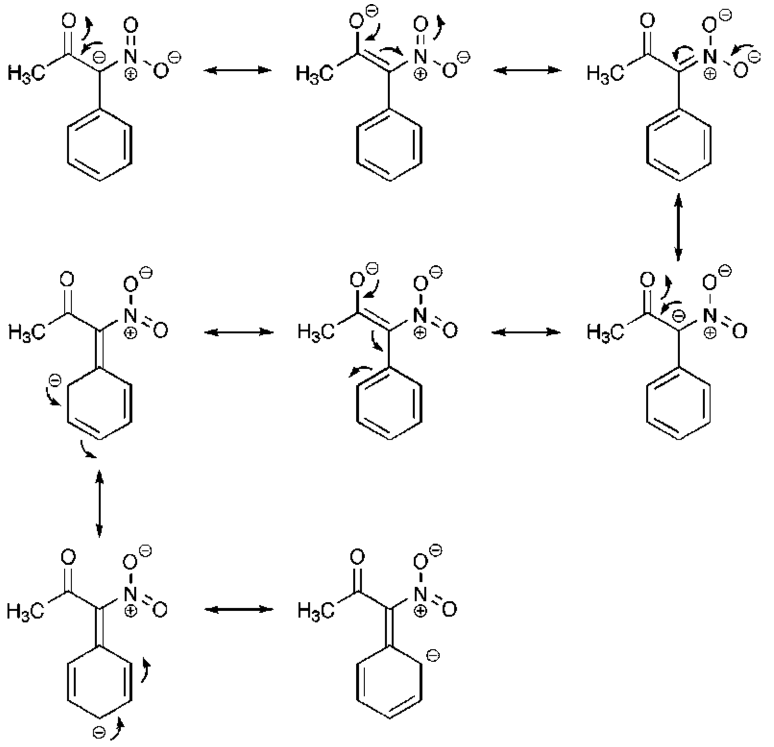


Please note that while nitro groups are so electron withdrawing that delocalization of their associated positive charge plays a minimal role in any family of resonance structures, this delocalization is technically possible. Try to identify additional resonance structures where the positive charge is delocalized.

f.

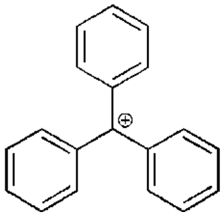


The following represent the resonance forms of the 3-nitroacetophenone anion:

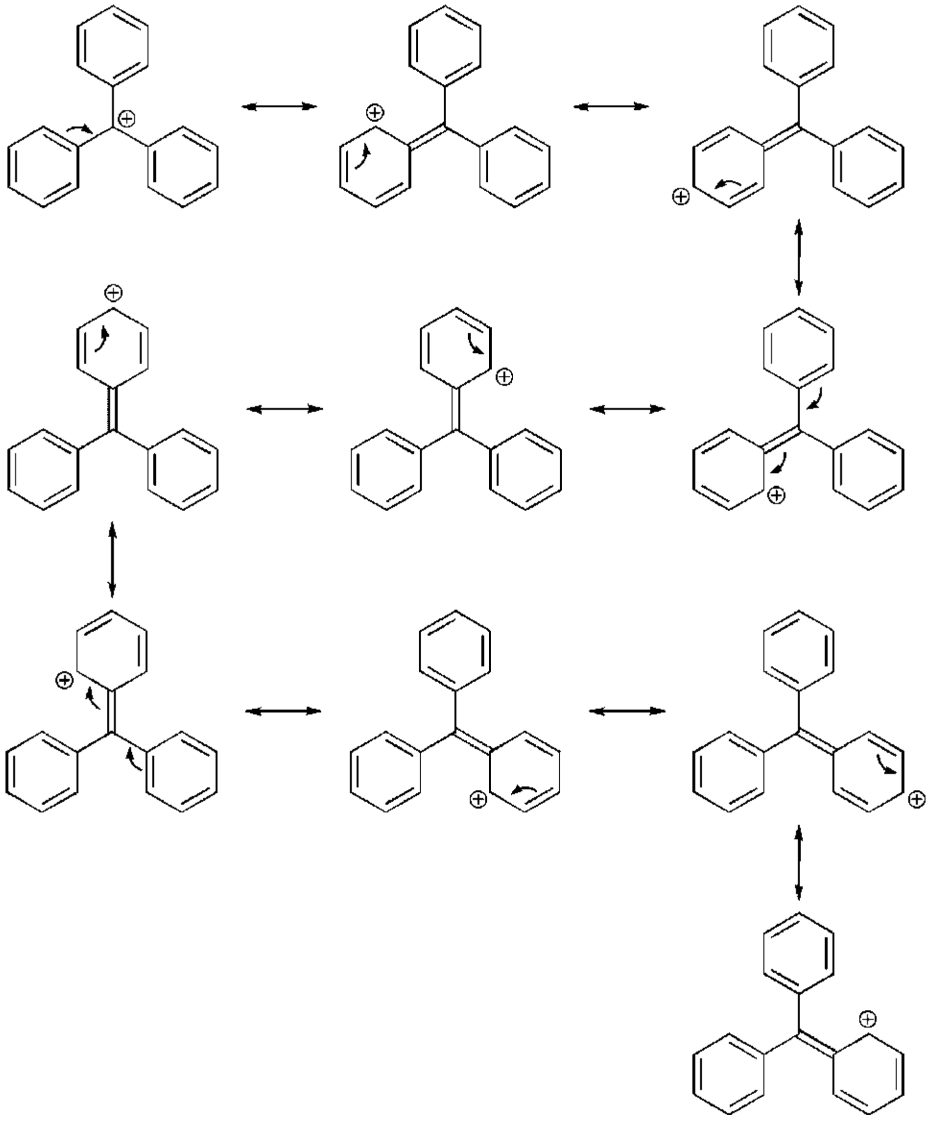


Please note that while nitro groups are so electron withdrawing that delocalization of their associated positive charge plays a minimal role in any family of resonance structures, this delocalization is technically possible. Try to identify additional resonance structures where the positive charge is delocalized.

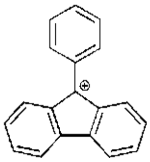
g.



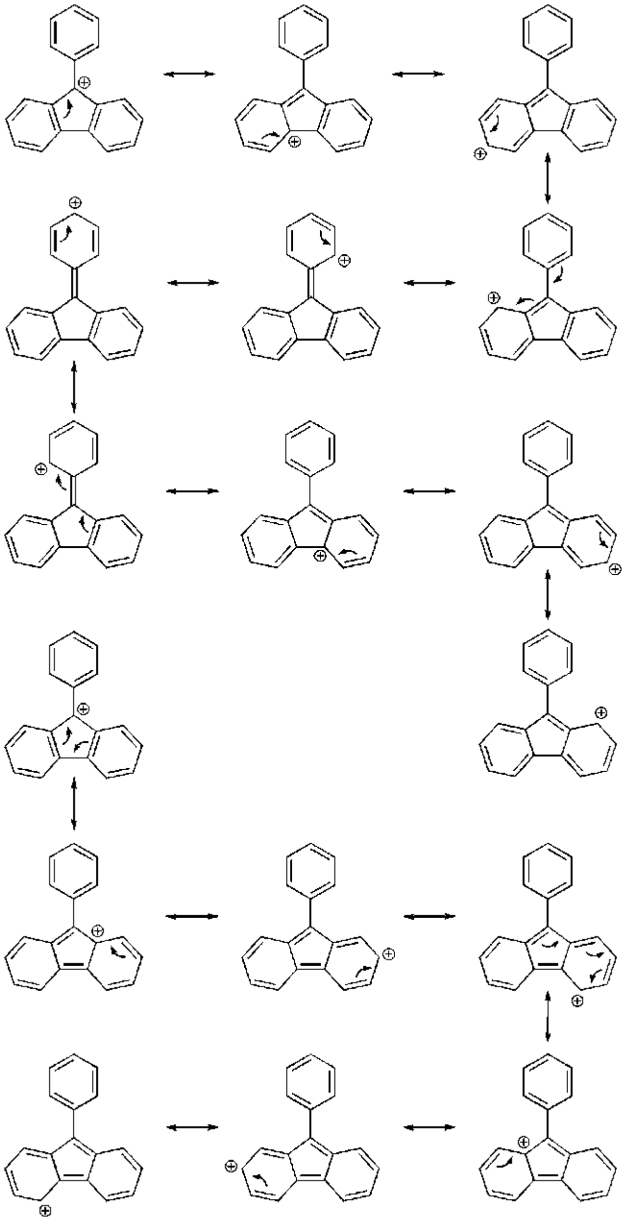
The following represent the resonance forms of the triphenylmethyl cation:



h.

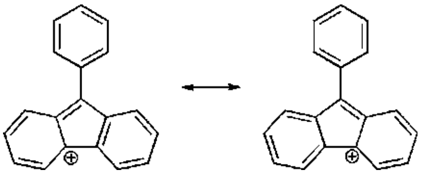


The following represent the resonance forms of the phenylfluorenyl cation:



4. *Which cation from Problem 3 is more stable, (**g**) or (**h**)? Explain using partial charges.*

Of the 16 resonance forms of the triphenylmethyl cation shown in the solution for Problem 3(**g**), no two resonance forms place the positive charge on adjacent atoms. However, when looking at the 16 resonance forms of the phenylfluorenyl cation shown in the solution for Problem 3(**h**), there are multiple pairs of resonance forms (one of which is shown below) where the positive charge may be placed on adjacent atoms. This is a disfavored electronic relationship and is destabilizing to the cation itself. Thus, through charge distribution and delocalization, because the phenylfluorenyl cation possesses partial positive charges on two adjacent atoms, the triphenylmethyl cation [Problem 3(**g**)] is more stable.

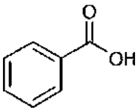


Note: There is another explanation relating to the definitions of aromatic and antiaromatic ring systems. See if you can explain the answer to this problem using these definitions.

5. *How will the following substituents affect the pK_a of benzoic acid (raise, lower, or no change)? Explain using partial charges to illustrate inductive effects. Remember,* o *refers to ortho positions,* m *refers to meta positions, and* p *refers to the para position.* ***In addressing these problems, assume that the acidity of the carboxylic acid is influenced solely by the partial charges induced by additional ring substituents.***

Note: It is important to realize that in addition to inductive effects, there are other factors that influence acidity and pK_a values. Therefore, while this problem asks for expectations regarding how ***inductive effects*** influence pK_a values, in actuality, the measured values may be different than anticipated.

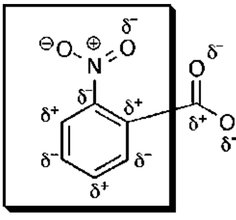
The pK_a of benzoic acid is 4.19



Benzoic Acid

a. o-NO_2

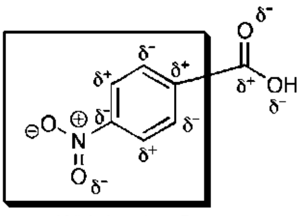
The structure of *o*-nitrobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *ortho* to the carboxylic acid, electron density is reduced adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *ortho* to the nitro group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *o*-nitrobenzoic acid is 2.16, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

b. p-NO_2

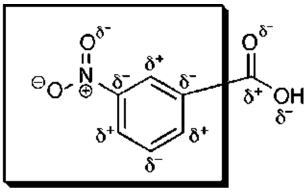
The structure of *p*-nitrobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *para* to the carboxylic acid, electron density is reduced adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *para* to the nitro group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *p*-nitrobenzoic acid is 3.41, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

c. m-NO_2

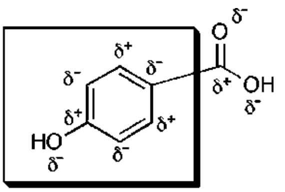
The structure of *m*-nitrobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *meta* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *meta* to the nitro group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *m*-nitrobenzoic acid is 3.47, reflecting the electron-withdrawing nature of the nitrophenyl group. While this value does not strictly support the conclusion of this problem, the trend, compared to Problems 5(a) and 5(b), indicates that the *m*-NO_2 has less of an effect on acidity than *o*-NO_2 and *p*-NO_2. In fact, NO_2 groups are so electron-withdrawing that they render the phenyl ring electron-withdrawing in its entirely.



Electron-Withdrawing Group
(Regardless of Partial Charges)

d. p-*OH*

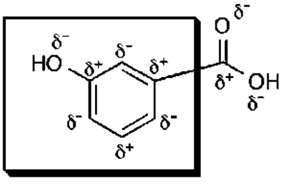
The structure of *p*-hydroxybenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating hydroxy group is located *ortho* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the hydroxyl group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-hydroxybenzoic acid is 4.48, thus supporting the conclusion of this problem.



Electron-Donating Group

e. m-*OH*

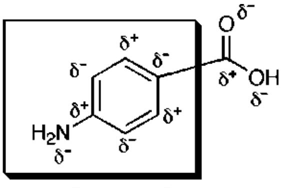
The structure of *m*-hydroxybenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating hydroxy group is located *meta* to the carboxylic acid, electron density is decreased adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the hydroxyl group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-hydroxybenzoic acid is 4.06, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

f. p-*NH_2*

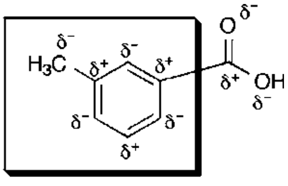
The structure of *p*-aminobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating amino group is located *para* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the amino group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-aminobenzoic acid is 4.65, thus supporting the conclusion of this problem.



Electron-Donating Group

g. m-*CH_3*

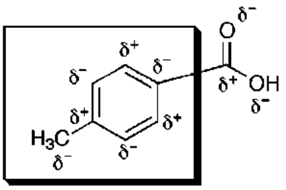
The structure of *m*-methylbenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating methyl group is located *meta* to the carboxylic acid, electron density is decreased adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the methyl group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-methylbenzoic acid is 4.27. In fact, because methyl groups are electron-donating, they render the phennyl ring weakly electron-donating in its entirety.



Electron-Donating Group
(Regardless of Partial Charges)

h. p-*CH_3*

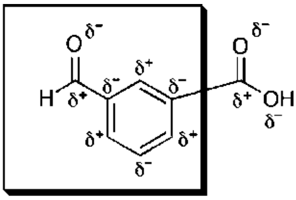
The structure of *p*-methylbenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating methyl group is located *para* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the methyl group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-methylbenzoic acid is 4.36, thus supporting the conclusion of this problem.



Electron-Donating Group

i. m-*CHO*

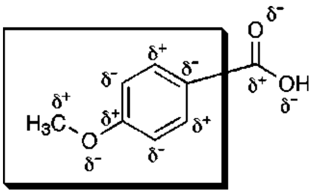
The structure of *m*-carboxybenzaldehyde is shown below with partial charges assigned to the ring system. Because the electron-withdrawing aldehyde group is located *meta* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *meta* to the carboxy (aldehyde) group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *m*-formylbenzoic acid is 3.85, reflecting the electron-withdrawing nature of the carboxyphenyl group. In fact, formyl groups (aldehydes) are so electron-withdrawing that they render the phenyl ring electron-withdrawing in its entirety.



Electron-Withdrawing Group
(Regardless of Partial Charges)

j. p-*OCH₃*

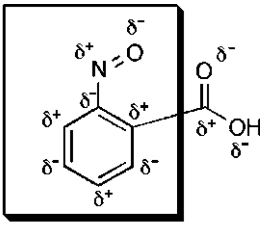
The structure of *p*-methoxybenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating methoxy group is located *para* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the methoxy group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-methoxybenzoic acid is 4.47, thus supporting the conclusion of this problem.



Electron-Donating Group

k. o-*NO*

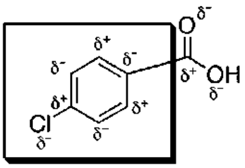
The structure of *o*-nitrosobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitroso group is located *ortho* to the carboxylic acid, electron density is reduced adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *ortho* to the nitroso group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *o*-nitrosobenzoic acid is <4, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

l. p-*Cl*

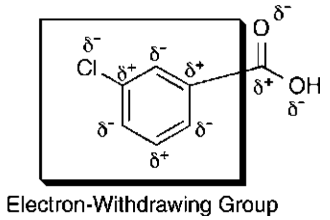
The structure of *p*-chlorobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating chloro group is located *para* to the carboxylic acid, electron density is increased adjacent to the acid functionality, effectively rendering the aromatic ring electron donating *para* to the chloro group. An electron-donating group attached to a carboxylic acid destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-chlorobenzoic acid is 3.98, reflecting the electron-withdrawing nature of the chlorophenyl group.



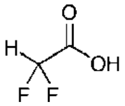
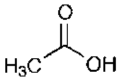
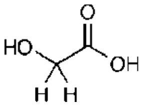
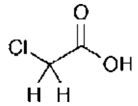
Electron-Withdrawing Group
(Regardless of Partial Charges)

m. m-*Cl*

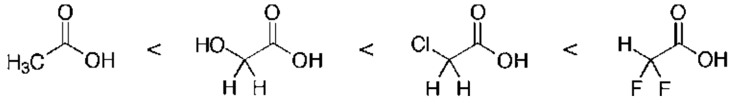
The structure of *m*-chlorobenzoic acid is shown below with partial charges assigned to the ring system. Because the electron-donating chloro group is located *meta* to the carboxylic acid, electron density is decreased adjacent to the acid functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the chloro group. An electron-withdrawing group attached to a carboxylic acid stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-chlorobenzoic acid is 3.82, thus supporting the conclusion of this problem.



6. *Arrange the following groups of molecules in order of increasing acidity. Explain your results using partial charges and inductive effects.*

Initially, when considering inductive effects, we realize that F, O, and Cl all possess partial negative charges. Therefore, we realize that all of these atoms will pull electron density from the carboxylic acid, thus stabilizing the anion resulting from deprotonation and lowering the pK_a values compared to the baseline acetic acid. The question now focuses on how strong this effect is for each atom. The answer is found in the periodic table of the elements and relates to electronegativities. Of the three atoms in question, F is the most electronegative. Moving to the second row, Cl is more electronegative than O. Since the most acidic compound will have the most electronegative atoms associated with it, the order of increasing acidity is as follows:

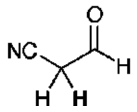


7. *Predict* pK_a *values for the protons shown in boldface in the following molecules. Rationalize your answers.*

When estimating the pK_a values for protons adjacent to multiple functional groups, the pK_a values can be calculated according to the following formula where *n* is defined as the number of relevant functional groups:

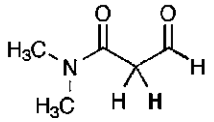
$$pK_a = \frac{\frac{pK_a^1}{n} + \frac{pK_a^2}{n} + \cdots + \frac{pK_a^n}{n}}{n}$$

a.



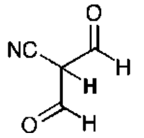
According to Appendix 1, the pK_a value for a proton adjacent to a nitrile is approximately 20–25, as is the pK_a value for a proton adjacent to an aldehyde. Recognizing that there are two relevant functional groups (an aldehyde and a nitrile), the above formula gives us a pK_a value of approximately 10–12.5.

b.



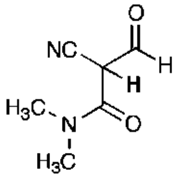
According to Appendix 1, the pK_a value for a proton adjacent to an amide is approximately 30–35, and the pK_a value for a proton adjacent to an aldehyde is approximately 20–25. Recognizing that there are two relevant functional groups (an aldehyde and an amide), the above formula gives us a pK_a value of approximately 12.5–15.

c.



According to Appendix 1, the pK_a value for a proton adjacent to a nitrile is approximately 20–25, as is the pK_a value for a proton adjacent to an aldehyde. Recognizing that there are three relevant functional groups (two aldehydes and a nitrile), the above formula gives us a pK_a value of approximately 6.7–8.3.

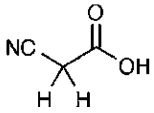
d.



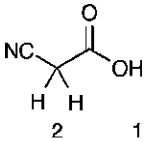
According to Appendix 1, the pK_a value for a proton adjacent to an amide is approximately 30–35, the pK_a value for a proton adjacent to an aldehyde is approximately 20–25 and the pK_a value for a proton adjacent to a nitrile is approximately 20–25. Recognizing that there are three relevant functional groups (a nitrile, an aldehyde, and an amide), the above formula gives us a pK_a value of approximately 7.8–9.4.

8. *Predict the order of deprotonation of the various protons in the following molecules. Back up your answers with appropriate* pK_a *values.*

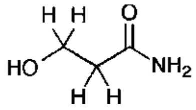
a.



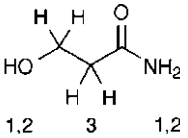
According to Appendix 1, the pK_a value for a carboxylic acid is approximately 4.75. Furthermore, if we imagine converting the carboxylic acid to an ester, we recognize that protons adjacent to esters have p*K*a values of approximately 25–30. Finally, the pK_a value for a proton adjacent to a nitrile is approximately 20–25. Using the formula described in Problem 7, we calculate a pK_a value of approximately 11.25–13.75 for the protons between the two functional groups. Therefore, the order of deprotonation is as follows:



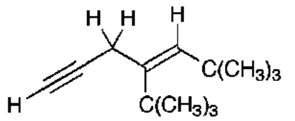
b.



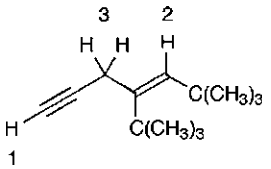
According to Appendix 1, the pK_a value for an amide is approximately 15–17, the pK_a of a primary alcohol is approximately 15–16, and the pK_a of a proton adjacent to an amide is approximately 30–35. Therefore, the order of deprotonation is as follows:



c.

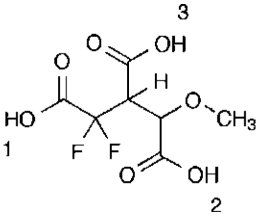


According to Appendix 1, the pK_a value for an acetylene is approximately 25, and the pK_a of a vinyl proton is approximately 35–40. While the acetylene and olefin lend delocalization effects to adjacent anions, the absence of heteroatoms incorporated in these functional groups minimizes this effect, and the pK_a at this position will resemble something between a vinyl pK_a and a hydrocarbon pK_a. Therefore, the order of deprotonation is as follows:

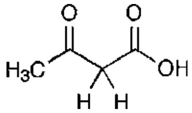


d.

This problem relies entirely on inductive effects. Realizing that fluorine is more electronegative than oxygen, the order of deprotonation is as follows:



9. *Which proton is the most acidic? Rationalize your answer.*



The pK_a value of a proton adjacent to a ketone carbonyl is approximately 20–25. The pK_a value of a carboxylic acid is approximately 4.75. Using the same calculations presented in the solution for Problem 8(a), the pK_a value of the protons between the ketone and the carboxylic acid is approximately 11.25–13.75. Since the acidity of a proton increases as its pK_a value decreases, the most acidic proton belongs to the carboxylic acid.

10. *Using the* pK_a *values given in Appendix 1, calculate the equilibrium constants for the following reactions:*

Recall from general chemistry that the equilibrium constant, K_{eq}, for a given reaction is defined as

$$A + B \rightleftharpoons C + D$$

$$K_{eq} = \frac{[C][D]}{[A][B]}$$

Also, recall that the definition of the acid dissociation constant, K_a, is

$$AH \rightleftharpoons A^- + H^+$$

$$K_a = \frac{[A^-][H^+]}{[AH]}$$

Finally, we recognize, as shown, that an acid–base equilibrium consists of two related reactions for which K_a values can be calculated and that at equilibrium, the $[H^+]$ is equivalent for each equation.

$$AH + B^- \rightleftharpoons A^- + BH$$

$$AH \rightleftharpoons A^- + H^+$$

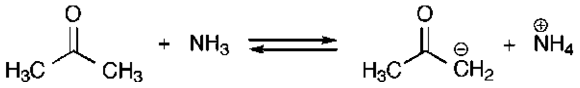
$$H^+ + B^- \rightleftharpoons BH$$

Therefore, with K_a^1 and K_a^2 defined, K_{eq} is derived as shown:

$$K_{eq} = \frac{K_a^1}{K_a^2} = \frac{\dfrac{[A^-][H^+]}{[AH]}}{\dfrac{[B^-][H^+]}{[BH]}} = \frac{[A^-][H^+][BH]}{[B^-][H^+][AH]} = \frac{[A^-][BH]}{[B^-][AH]}$$

and K_{eq} is simply the ratio of the two relevant K_a values.

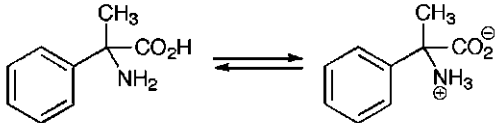
a.



From Appendix 1, we know that pK_a^1, the dissociation constant associated with protons adjacent to ketone carbonyls, is approximately 20–25. Furthermore, from Appendix 1, we know that pK_a^2, the dissociation constant associated with protonated amines, is approximately 10. Finally, remembering that p$K_a = -\log K_a$, the K_{eq} for this reaction ranges from

$$\frac{10^{-20}}{10^{-10}} \text{ to } \frac{10^{-25}}{10^{-10}} \quad \text{or} \quad 10^{-10} \text{ to } 10^{-15}$$

b.



From Appendix 1, we know that pK_a^1, the dissociation constant associated with carboxylic acid protons, is approximately 4.75. Furthermore, from Appendix 1, we know that pK_a^2, the dissociation constant associated with protonated amines, is approximately 10. Finally, remembering that p$K_a = -\log K_a$, the K_{eq} for this reaction is approximately

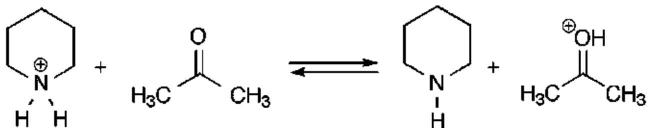
$$\frac{10^{-4.75}}{10^{-10}} \quad \text{or} \quad 10^{5.25}$$

c. $\mathrm{HCl} + \mathrm{Br}^{\ominus} \rightleftharpoons \mathrm{HBr} + \mathrm{Cl}^{\ominus}$

From Appendix 1, we know that pK_a^1, the dissociation constant associated with hydrochloric acid, is approximately −2.2. Furthermore, from Appendix 1, we know that pK_a^2 the dissociation constant associated with hydrobromic acid, is approximately −4.7. Finally, remembering that p$K_a = -\log K_a$, the K_{eq} for this reaction is approximately

$$\frac{10^{-2.2}}{10^{-4.7}} \quad \text{or} \quad 10^{-2.5}$$

d.



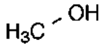
From Appendix 1, we know that $\mathrm{p}K_a^1$, the dissociation constant associated with protonated amines, is approximately 10. Furthermore, from Appendix 1, we know that $\mathrm{p}K_a^2$, the dissociation constant associated with protonated ketones, is approximately -7 to -9. Finally, remembering that $\mathrm{p}K_a = -\log K_a$, the K_{eq} for this reaction ranges from

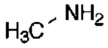
$$\frac{10^{-10}}{10^{7}} \text{ to } \frac{10^{-10}}{10^{9}} \quad \text{or} \quad 10^{-17} \text{ to } 10^{-19}$$

CHAPTER 3 SOLUTIONS

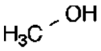
1. *In each case, circle the better nucleophile. Explain your answers.*

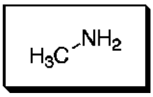
a.





Oxygen is more electronegative than nitrogen. Therefore, the lone pair on nitrogen is not held as tightly as the lone pairs of oxygen. This greater availability of the nitrogen lone pair compared to the oxygen lone pairs makes the amine the better nucleophile.





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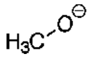
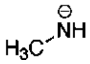
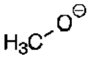
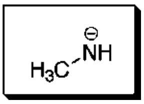




Oxygen is more electronegative than nitrogen. This difference in electronegativity is reflected in the greater acidity of alcohols compared to amines. As oxygen lone pairs are held more tightly than the nitrogen lone pair, negative charges on oxygen are more stable than negative charges in nitrogen. Thus, the nitrogen anion is more available to react, making it the better nucleophile.





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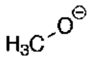
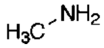
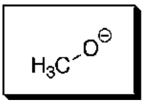
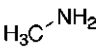




While in equivalent states, nitrogen functionalities are better nucleophiles than oxygen nucleophiles [see Problem 1(a) and 1(b)], when comparing different electronic states, the more reactive species will be the better nucleophile. Thus, the oxygen anion is the better nucleophile compared to an amine.





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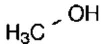
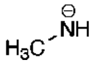
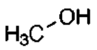
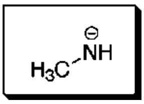




For all the reasons discussed under Problem 1(a), 1(b), and 1(c), the nitrogen anion is the better nucleophile.





e. $Cl^{\ominus}$ $I^{\ominus}$

The answer to this question depends on the solvent used for reaction as illustrated in Figure 3.4. Also relevant is recognition that chloride anions are hard bases and iodide anion are soft bases. Iodide is the better nucleophile in polar protic solvents while chloride is the better nucleophile in polar aprotic solvents.

f. $N\equiv C^{\ominus}$ $HC\equiv C^{\ominus}$

As shown in Appendix 1, the pK_a value for hydrocyanic acid is approximately 9.3, and the pK_a value for acetylene is approximately 25. Thus, the acetylene anion is more reactive than the cyanide anion and is therefore the better nucleophile.

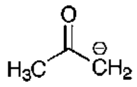
$N\equiv C^{\ominus}$ $\boxed{HC\equiv C^{\ominus}}$

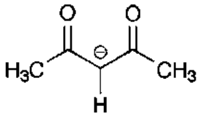
g. $H_3C^{\ominus}$ $N\equiv C-\overset{\ominus}{C}H_2$

As shown in Appendix 1, the pK_a value for methane is approximately 50–75, and the pK_a value for acetonitrile is approximately 25. Thus, the methyl anion is more reactive than the acetonitrile anion and is therefore the better nucleophile.

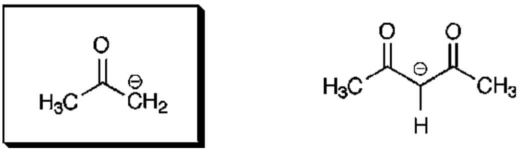
$\boxed{H_3C^{\ominus}}$ $N\equiv C-\overset{\ominus}{C}H_2$

h.

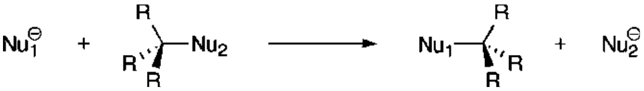




As shown in Appendix 1, the pK_a value for acetone is approximately 20. Furthermore, the pK_a value for acetylacetone is approximately 10 as estimated using the formula presented in Chapter 2, Problem 7. Thus, the acetone anion is more reactive than the acetylacetone anion and is therefore the better nucleophile.



2. *Nucleophiles often participate in nucleophilic substitution reactions. The general form of these reactions may be represented by the following equation where Nu_1^- and Nu_2^- are nucleophiles*:



   a. *Explain what type of relationship between, Nu_1^- and Nu_2^- is necessary in order for this reaction to be favored.*

      In order for this reaction to proceed, Nu_1^- must be a better nucleophile than Nu_2^-.

   b. *What does this say about the relative bacisities of Nu_1^- and Nu_2^-?*

      In general the stronger nucleophile is also the stronger base. Therefore, Nu_1^- is more basic than Nu_2^-.

   c. *Which nucleophile has the larger pK_a?*

      Remembering that a strong base is derived from a weak conjugate acid, if we consider the conjugate acids of Nu_1^- and Nu_2^-, we expect that since Nu_1^- is more basic, its conjugate acid has the larger pK_a than the conjugate acid of Nu_2^-.

   d. *What generalization can be concluded about the relationship between bases and nucleophiles?*

      Since nucleophiles, by definition, are species attracted to positive charges and since, by definition, protons are positively charged, nucleophiles are bases. The extent of nucleophilicity associated with a given nucleophile largely depends on the degree of its basicity. Thus, in general terms, the more nucleophilic a given nucleophile, the more basic it is.

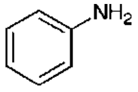
3. *How can pK_a values be used to describe basicity?*

By definition, pK_a values relate to the degree of acidity associated with a given acid. Referring to the Henderson–Hesselbach equation, as acidity increases, pK_a values decrease. Conversely, as acidity decreases, pK_a values increase. Referring to the definition of a base, we realize that as acidity increases, basicity decreases. Conversely, as acidity decreases, basicity increases. Recognizing that as acidity decreases, pK_a values increase, we recognize that as pK_a values increase, basicity increases. Therefore, the higher the pK_a value, the greater the basicity and the lower the pK_a value, the lower the basicity.

4. *As electron-donating and electron-withdrawing substituents will affect the acidity of organic molecules, so will they affect the basicity. How will the following substituents affect (raise, lower, or no change) the* pK_a *of aniline (aminobenzene)? Explain using partial charges to illustrate inductive effects. Remember,* o *refers to ortho positions,* m *refers to meta positions, and* p *refers to the para position.* ***In addressing these problems, assume that the acidity of the amine is influenced solely by the partial charges induced by additional ring substituents.***

Note: It is important to realize that, in addition to inductive effects, there are other factors that influence acidity and pK_a values. Therefore, while this problem asks for expectations regarding how **inductive effects** influence pK_a values, in actuality, the measured values may be different than anticipated.

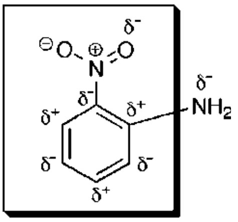
The pK_a of aniline is 4.63



aniline

a. o-NO_2

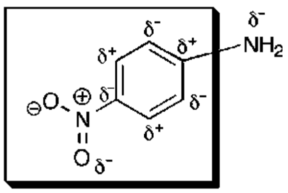
The structure of *o*-nitroaniline is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *ortho* to the amine, electron density is reduced adjacent to the amine functionality, effectively rendering the aromatic ring electron withdrawing *ortho* to the nitro group. An electron-withdrawing group attached to an amine stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *o*-nitroaniline is -0.26, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

b. p-NO_2

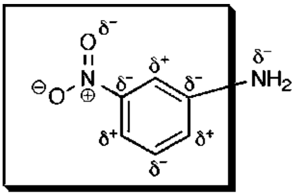
The structure of *p*-nitroaniline is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *para* to the amine, electron density is reduced adjacent to the amine functionality, effectively rendering the aromatic ring electron withdrawing *para* to the nitro group. An electron-withdrawing group attached to an amine stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *p*-nitroaniline is 1.0, thus supporting the conclusion of this problem.



Electron-Withdrawing Group

c. m-NO_2

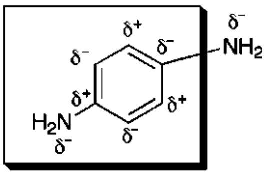
The structure of *m*-nitroaniline is shown below with partial charges assigned to the ring system. Because the electron-withdrawing nitro group is located *meta* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *meta* to the nitro group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *m*-nitroaniline is 2.47, thus supporting the conclusion of this problem reflecting the electron-withdrawing nature of the nitrophenyl group. While this value does not strictly support the conclusion of this problem, the trend, compared to Problems 4(a) and 4(b), indicates that the *m*-NO_2 has less of an effect on acidity than *o*-NO_2 and *p*-NO_2. In fact, NO_2 groups are so electron-withdrawing that they render the phenyl ring electron-withdrawing in its entirety.



Electron-Withdrawing Group
(Regardless of Partial Charges)

d. p-NH_2

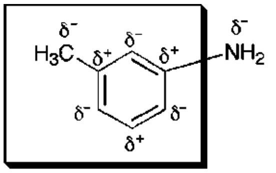
The structure of *p*-aminoaniline is shown below with partial charges assigned to the ring system. Because the electron-donating amino group is located *para* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *para* to the amino group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-phenylenediamine is 6.2, thus supporting the conclusion of this problem.



Electron-Donating Group

e. m-*CH_3*

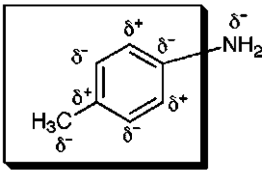
The structure of *m*-methylaniline is shown below with partial charges assigned to the ring system. Because the electron-donating methyl group is located *meta* to the amine, electron density is decreased adjacent to the amine functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the methyl group. An electron-withdrawing group attached to an amine stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-methylaniline is 4.73. In fact, because methyl groups are electron-donating, they render the phenyl ring weakly electron-donating in its entirety.



Electron-Donating Group
(Regardless of Partial Charges)

f. p-*CH_3*

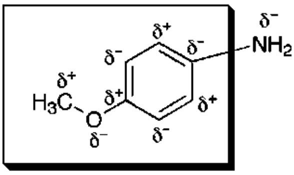
The structure of *p*-methylaniline is shown below with partial charges assigned to the ring system. Because the electron-donating methyl group is located *para* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *para* to the methyl group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-methylaniline is 5.08, thus supporting the conclusion of this problem.



Electron-Donating Group

g. p-*OCH_3*

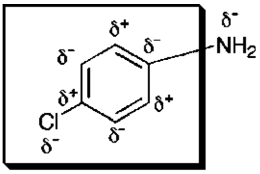
The structure of *p*-methoxyaniline is shown below with partial charges assigned to the ring system. Because the electron-donating methoxy group is located *para* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *para* to the methoxy group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-methoxyaniline is 5.34, thus supporting the conclusion of this problem.



Electron-Donating Group

h. p-*Cl*

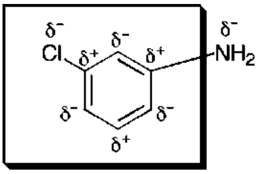
The structure of *p*-chloroaniline is shown below with partial charges assigned to the ring system. Because the electron-donating chloro group is located *para* to the amine, electron density is increased adjacent to the amine functionality, effectively rendering the aromatic ring electron donating *para* to the chloro group. An electron-donating group attached to an amine destabilizes the anion resulting from deprotonation, thus decreasing its acidity and *raising* its pK_a. In actuality, the pK_a of *p*-chloroaniline is 4.15, reflecting the electron-withdrawing nature of the chlorophenyl group.



Electron-Withdrawing Group
(Regardless of Partial Charges)

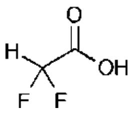
i. m-*Cl*

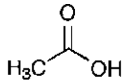
The structure of *m*-chloroaniline is shown below with partial charges assigned to the ring system. Because the electron-donating chloro group is located *meta* to the amine, electron density is decreased adjacent to the amine functionality, effectively rendering the aromatic ring electron withdrawing *meta* to the chloro group. An electron-withdrawing group attached to an amine stabilizes the anion resulting from deprotonation, thus increasing its acidity and *lowering* its pK_a. In actuality, the pK_a of *m*-chloroaniline is 3.46, thus supporting the conclusion of this problem.

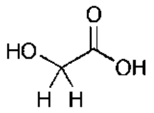


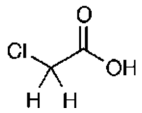
Electron-Withdrawing Group

5. *Arrange the following groups of molecules in order of increasing basicity. Explain your results using partial charges and inductive effects.*

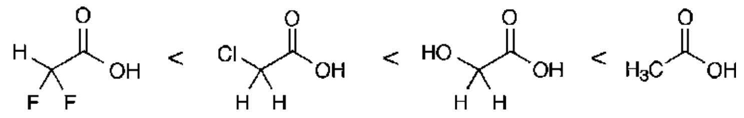








Initially, when considering inductive effects, we realize that F, O, and Cl all possess partial negative charges. Therefore, we realize that all of these atoms will pull electron density from the carboxylic acid, thus stabilizing the anion resulting from deprotonation and lowering the pK_a values compared to the baseline acetic acid. The question now focuses on how strong this effect is for each atom. The answer is found in the periodic table of the elements and relates to electronegativities. Of the three atoms in question, F is the most electronegative. Moving to the second row, Cl is more electronegative than O. Since the most basic compound will have the least electronegative atoms associated with it, the order of increasing basicity is as follows:

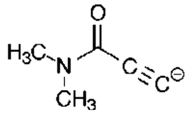


Note that this is the opposite sequence as that presented in Chapter 2, Problem 6.

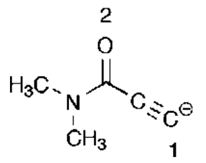
6. *Predict the order of protonation of the basic sites on the following molecules. Support your answers with* pK_a *values.*

In addressing this problem, it is important to recognize that the order of protonation depends upon the basicity associated with the respective functional groups. As discussed above, basicity can be relayed back to the pK_a values associated with the conjugate acids of the respective sites of protonation. Thus conjugate acids with the higher pK_a values will be protonated first while conjugate acids with lower pK_a values will be protonated last.

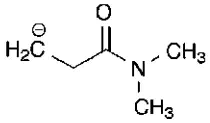
a.



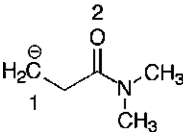
According to Appendix 1, the pK_a value for an acetylene proton is approximately 25, and the pK_a value for a carbonyl-protonated amide is approximately 0. Therefore, the order of protonation is as follows:



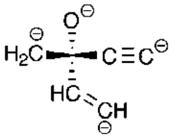
b.



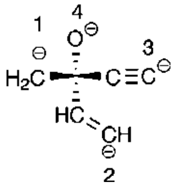
According to Appendix 1, the pK_a value for an alkane proton is approximately 50–75, and the pK_a value for a carbonyl-protonated amide is approximately 0. Therefore, the order of protonation is as follows:



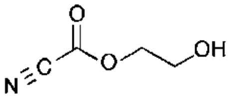
c.



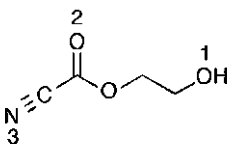
According to Appendix 1, the pK_a value for an alkane proton is approximately 50–75, the pK_a value for a vinyl proton is approximately 35–40, the pK_a value for an acetylene proton is approximately 25, and the pK_a value for an alcohol is approximately 15–19. Therefore, the order of protonation is as follows:



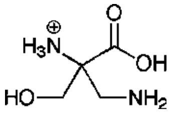
d.



According to Appendix 1, the pK_a value for a protonated nitrile is approximately −10, the pK_a value for a carbonyl-protonated ester is approximately −6, and the pK_a value for a protonated alcohol is approximately −2. Therefore, the order of protonation is as follows:



7. *Which proton is the least acidic? Explain your answer.*

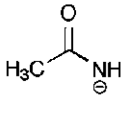


The pK_a value associated with carboxylic acid is approximately 4.75. The pK_a value of a primary alcohol is approximately 16. The pK_a value of an amine is approximately 35. The pK_a value of a protonated amine is approximately 10. Since the highest pK_a value belongs to the amine, protons associated with the amine functionality are the least acidic.

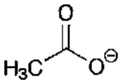
8. *Separate the following group of bases into a group of hard bases and a group of soft bases. Rationalize your answers based on electronegativity and polarizability.*

$H_3C-O^{\ominus}$ $H_3C-S^{\ominus}$ $I^{\ominus}$

$H_3C-\overset{\ominus}{N}H$ $F^{\ominus}$



$Cl^{\ominus}$



$Br^{\ominus}$

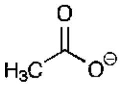
$^{\ominus}N=\overset{\oplus}{N}=N^{\ominus}$

As a general rule, the basic atoms associated with soft bases have lower electronegativities and are more polarizable. Likewise, the basic atoms associated with hard bases have higher electronegativities and are less polarizable. Therefore, using the periodic table of the elements, the group of bases listed above can be separated as illustrated.

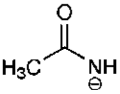
Hard

$F^{\ominus}$ $^{\ominus}N=\overset{\oplus}{N}=N^{\ominus}$

$Cl^{\ominus}$ $H_3C-O^{\ominus}$



$H_3C-\overset{\ominus}{N}H$



Soft

$Br^{\ominus}$

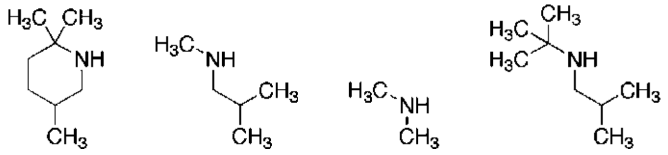
$I^{\ominus}$

$H_3C-S^{\ominus}$

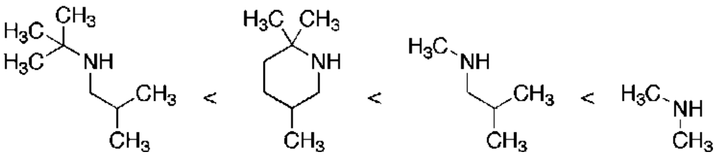
9. *Arrange the following structures in order of increasing nucleophilicity:*

When a nucleophilic atom is surrounded by additional substituents, the degree of nucleophilicity is altered. This observation is explained because nucleophilicity depends, in part, on the ability of a given nucleophile to react with electrophiles. If the nucleophilic atom cannot approach the electrophile because of steric congestion surrounding the nucleophilic atom, then the nucleophile is rendered less effective as a nucleophile and more effective as a base.

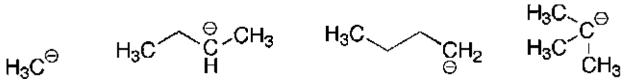
a.



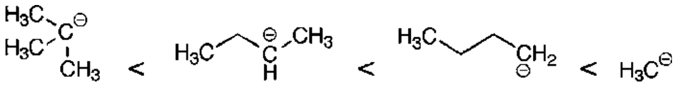
Based on the above argument, the order of increasing nucleophilicity for this group of amines is shown below. Regarding the first two amines, the piperidine is more nucleophilic because, unlike *tert*-butyl isobutylamine, the alkyl groups are tied back into a ring and not able to move. This allows the nitrogen to more readily present its lone pair.



b.



Based on the above argument, the order of increasing nucleophilicity for this group of alkyl anions is shown below.



10. *For the following pairs of structures, circle the better leaving group.*

a. $Cl^{\ominus}$ $I^{\ominus}$

Compared to the chloride ion, the iodide ion is less electronegative and more polarizable. This polarizability stabilizes the anion as is reflected in the pK_a value for hydroiodic acid (−10) compared to the pK_a value for hydrochloric acid (−2.2). Therefore, iodide is the better leaving group.

$$Cl^{\ominus} \qquad \boxed{I^{\ominus}}$$

b. $H_3C{-}O^{\ominus}$ $\qquad$ $H_3C{-}\overset{\ominus}{N}H$

Compared to nitrogen, oxygen is more electronegative and thus holds onto its electrons more tightly. This stabilization of the oxygen anion compared to the amine anion is reflected in the pK_a values for alcohols (15–19) compared to the pK_a value for amines (35). Therefore, the alkoxide is the better leaving group.

$$\boxed{H_3C{-}O^{\ominus}} \qquad H_3C{-}\overset{\ominus}{N}H$$

c. $CH_3CH_2{-}O^{\ominus}$ $\qquad$ $CF_3CH_2{-}O^{\ominus}$

When comparing leaving groups where the departing atoms are the same, inductive effects must be considered. Since fluorine is more electronegative than hydrogen, the presence of three fluorides pulls electron density from the alkoxide ion, thus stabilizing the anion. This is reflected in the pK_a values for trifluoroethanol (11–12) compared to the pK_a values for ethanol (15–16). Therefore, trifluoroethoxide is the better leaving group.

$$CH_3CH_2{-}O^{\ominus} \qquad \boxed{CF_3CH_2{-}O^{\ominus}}$$

d. $H_3C{-}S^{\ominus}$ $\qquad$ $H_3C{-}O^{\ominus}$

Compared to oxygen, sulfur is less electronegative and more polarizable. This increase in polarizability stabilizes the anion, as is reflected in the pK_a value for methanethiol (10.4) compared to the pK_a values for methanol (15–16). Therefore, the methylsulfide anion is the better leaving group.

$$\boxed{H_3C{-}S^{\ominus}} \qquad H_3C{-}O^{\ominus}$$

e. $F^{\ominus}$ $Br^{\ominus}$

Compared to the fluoride ion, the bromide ion is less electronegative and more polarizable. This polarizability stabilizes the anion, as is reflected in the pK_a value for hydrobromic acid (−4.7) compared to the pK_a value for hydrofluoric acid (3.18). Therefore, bromide is the better leaving group.

$F^{\ominus}$ $\boxed{Br^{\ominus}}$

f. $H_3C-\overset{\ominus}{N}H$ $H_3C-S^{\ominus}$

Like oxygen, sulfur is more electronegative than nitrogen. Additionally, sulfur is more polarizable. These differences stabilize the sulfur anion as reflected in the pK_a value for methyl sulfide (10.4) compare to the pK_a value for amines (35). Therefore, the methylsulfide anion is the better leaving group.

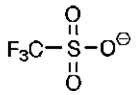
$H_3C-\overset{\ominus}{N}H$ $\boxed{H_3C-S^{\ominus}}$

g. $Br^{\ominus}$ $H_3C-O^{\ominus}$

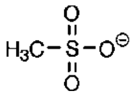
Bromine is more electronegative and more polarizable than oxygen. This translates to increased stability of the bromide anion compared to the oxygen anion. This stabilization is reflected in the pK_a value for hydrobromic acid (−4.7) compared to the pK_a values for methanol (15–16). Therefore, bromide is the better leaving group.

$\boxed{Br^{\ominus}}$ $H_3C-O^{\ominus}$

h.

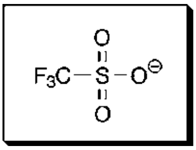


$F_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O^{\ominus}$

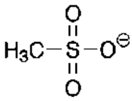


$H_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O^{\ominus}$

When comparing leaving groups where the departing atoms are the same, inductive effects must be considered. Since fluorine is more electronegative than hydrogen, the presence of three fluorides pulls electron density from the sulfonate ion, thus stabilizing the anion. This is the same effect noted under Problem 10(c). Therefore, trifluoromethane sulfonate is the better leaving group.



$$\boxed{F_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O^{\ominus}}$$

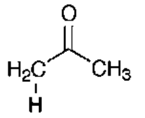


$$H_3C-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-O^{\ominus}$$

CHAPTER 4 SOLUTIONS

1. *In many S_N2 reactions, the nucleophile is generated by deprotonation of an organic acid. For each molecule, chose the base best suited to completely remove the labeled proton. (Consider pK_a values and recognize that, in some cases, dianions should be considered.) Explain your answers.*

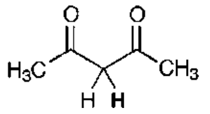
a.



$NaOCH_3 : (CH_3)_2NLi : CH_3Li$

The pK_a of the highlighted proton is approximately 20. Therefore, $NaOCH_3$ (pK_a of conjugate acid methanol = 16) is not a strong enough base. CH_3Li (pK_a of conjugate acid methane = 50) will deprotonate this molecule; however, it is too nucleophilic a base and will predominantly add to the carbonyl to produce a tertiary alcohol (see Chapter 7). $(CH_3)_2NLi$ (pK_a of conjugate acid dimethylamine = 35) is a bulkier base than CH_3Li and is, therefore, less nucleophilic and the best base for this case.

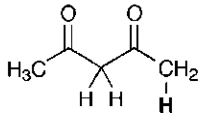
b.



$NaOCH_3 : (CH_3)_2NLi : CH_3Li$

The pK_a of the highlighted proton is approximately 12. As described in the answer for Problem 1(a), CH_3Li (pK_a of conjugate acid methane = 50) will deprotonate this molecule; however, it is too nucleophilic a base and will predominantly add to the carbonyls to produce tertiary alcohols (see Chapter 7). While $(CH_3)_2NLi$ (pK_a of conjugate acid dimethylamine = 35) is a bulkier base than CH_3Li and is, therefore, less nucleophilic, it is also more basic than required for removal of the specified proton. $NaOCH_3$ (pK_a of conjugate acid methanol = 16), on the other hand, is a milder base and, based on pK_a values, is adequate to fully deprotonate the illustrated compound.

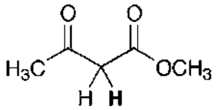
c.



$NaOCH_3 : (CH_3)_2NLi : CH_3Li$

In this case, the most acidic proton is not the proton of interest. Therefore, it is important to remember that once the most acidic proton is removed, the resulting enolate anion renders the proton of interest even less acidic because the enolate anion is less able to stabilize the second anion. Thus, removal of the desired proton will require a comparatively stronger base. Additionally, it is important to understand (as will be explained in Chapter 7), that a negative charge next to a carbonyl makes the carbonyl much less susceptible to nucleophilic attack. Therefore, once the most acidic proton is removed with $NaOCH_3$, removal of the desired proton can subsequently be achieved using CH_3Li.

d.

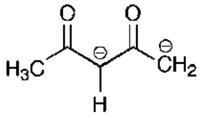


NaOH : NaOCH₃ : NaOCH₂CH₃

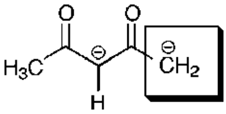
In this problem, three bases are presented that all possess comparable pK_a values and are all basic enough to remove the desired proton. In this case, however, the problem is not to recognize which base will remove the desired proton, but to understand the reactivity of the target molecule in the presence of the various bases. The specific functionality of concern is the methyl ester. While the chemistry of ester groups is discussed in the next chapter, using the principles of arrow pushing, the answer to this problem can be derived from information already presented. Specifically, if any one of these bases is used, addition to the ester, followed by subsequent elimination of the CH_3O^- group follows. This addition–elimination sequence produces a carboxylic acid, an ethyl ester, or a methyl ester. Since the starting molecule possesses a methyl ester, and since there is no instruction to change the nature of the ester, $NaOCH_3$ is the best base for this job.

2. *In predicting the course of S_N2 reactions, it is important to recognize groups most likely to act as nucleophiles. For each molecule, label the most nucleophilic site.*

a.



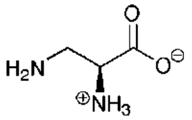
Considering the pK_a values of the respective conjugate acids, protons between two carbonyl groups have pK_a values around 12 while protons adjacent to only one carbonyl have pK_a values around 20. Therefore, the most nucleophilic site is



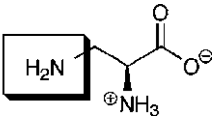
b.

Oxygen is more electronegative than nitrogen. As such, oxygen holds its lone pairs of electrons more tightly than does nitrogen. Therefore, the most nucleophilic site is

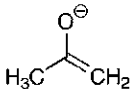
c.



Ammonium ions, having no available electron pairs, are not nucleophilic. Carboxylate anions are nucleophilic, but the anions are stabilized through delocalization of the negative charge, thus decreasing their nucleophilicity. As mentioned in Problem 2(b), nitrogen is less electronegative than oxygen. As the only oxygen atoms in this compound are associated with a stable carboxylate anion, the most nucleophilic site is

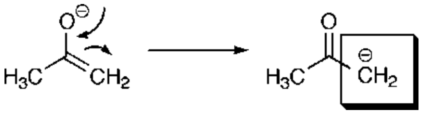


d.



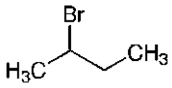
(Hint: Consider resonance.)

This structure represents an acyl anion with the negative charge delocalized to the oxygen. Since the carbon and the oxygen both possess partial negative charge characteristics, the degree of nucleophilicity depends upon the relative electronegativities of carbon versus oxygen. Since oxygen is more electronegative than carbon, the most nucleophilic site is

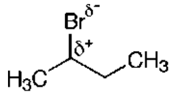


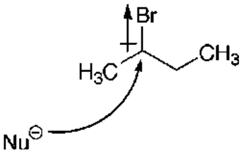
3. *For each molecule, show the partial charges, bond polarity, and where a nucleophile is most likely to react.*

a.

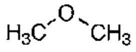


The polarity and partial charges of 2-bromobutane are dictated by the electronegativity of bromine versus the electronegativity of carbon. Therefore, the partial charges and polarity are as represented below, and a nucleophile is most likely to react at the carbon bearing the bromine atom.

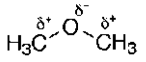


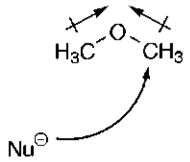


b.

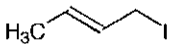


The polarity and partial charges of dimethyl ether are dictated by the electronegativity of oxygen versus the electronegativity of carbon. Therefore, the partial charges and polarity are as represented below, and a nucleophile is most likely to react at either of the carbon atoms.

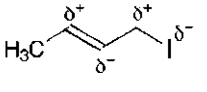


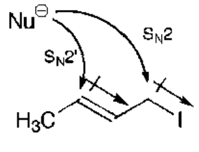


c.

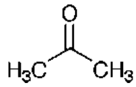


The polarity and partial charges of 1-iodo-2-butene are dictated by the electronegativity of oxygen versus the electronegativity of carbon. Additionally, delocalization through the double bond extends the chain of partial charges. Therefore, the partial charges and polarity are as represented below, and a nucleophile is most likely to react at either of the specified carbon atoms via an S_N2 or an S_N2' mechanism.



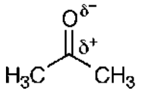


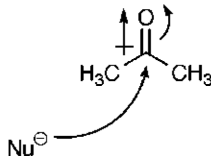
d.



The polarity and partial charges of acetone are dictated by the electronegativity of oxygen versus the electronegativity of carbon as associated with a carbonyl.

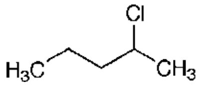
Therefore, the partial charges and polarity are as represented below, and a nucleophile is most likely to react at the carbonyl carbon as will be discussed in Chapter 7.



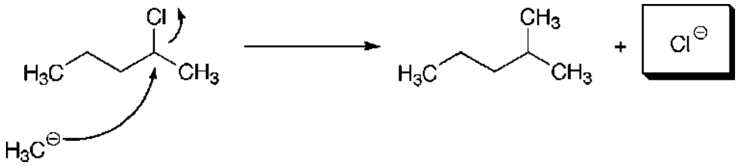


4. *For each molecule, identify the leaving group assuming that H_3C^- is the nucleophile.*

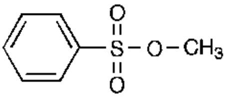
a.



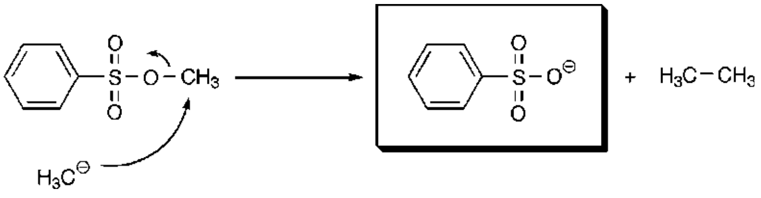
Applying partial charges based on the discussions presented in this chapter, the chlorine atom is recognized as the most electronegative. Therefore, as shown below, the chloride anion is the leaving group.



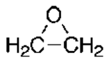
b.



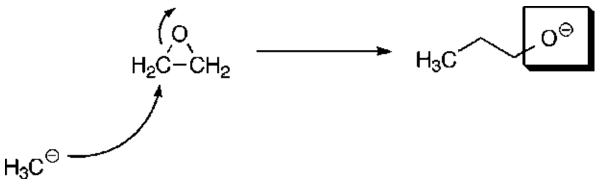
Applying partial charges based on the discussions presented in this chapter, the oxygen is recognized as more electronegative than carbon. Furthermore, an oxygen anion, derived from cleavage of a carbon–oxygen bond, is delocalized into the sulfur–oxygen double bonds and increasing its stability. Therefore, as shown below, the phenylsulfonate anion is the leaving group.



c.

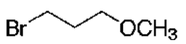


Applying partial charges based on the discussions presented in this chapter, the oxygen is recognized as more electronegative than carbon. Therefore, as shown below, the oxygen anion is the leaving group. Please note that in the case of an epoxide, the leaving group is attached to the reaction product.



5. *For each molecule, label the most likely leaving group. Explain your answers.*

a.



Bromine is more electronegative than oxygen. Furthermore, a bromide ion is a softer base than a methoxide ion. Because bromine can stabilize a negative charge better than oxygen, Br^- is the better leaving group.

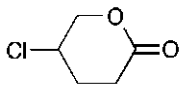
b.

Oxygen is more electrophilic than nitrogen. Therefore, $(CH_3)_2O$ is the better leaving group.

c.

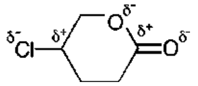
Bromide ions are softer bases than chloride ions. Therefore, bromine is more polarizable than chlorine, making Br^- the better leaving group.

d.

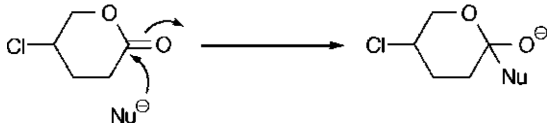


The answer to this question depends on information presented in Chapter 7. However, through an understanding of the nature of various nucleophiles coupled with application of arrow-pushing techniques, the answer can be derived from information presented thus far.

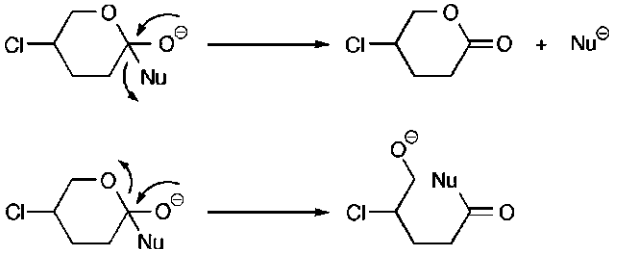
First, analyzing this structure for partial charges, we recognize the charge distribution as represented below.



Recognizing that nucleophiles can react at two different sites, an initial thought might be direct displacement of the chloride anion in an S_N2 manner. However, as alluded to in Problem 3(d), nucleophiles can add to carbonyl groups as shown below.



Once a nucleophile reacts with an ester carbonyl as shown above, the next phase of reaction depends on whether the better leaving group is an oxygen anion or the nucleophile itself. This is illustrated below through the ability of the newly formed oxygen anion to displace either the nucleophile or a second oxygen anion.

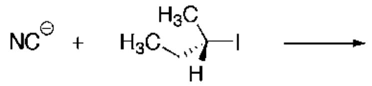


As shown above, if the better leaving group is the nucleophile, the result is regeneration of the starting material and the realization that displacement of Cl^- through an S_N2 mechanism is the most likely course of this reaction. However, if the better leaving group is the oxygen anion, then displacement of Cl^- generally will be a secondary reaction depending upon how much nucleophile is added to this system.

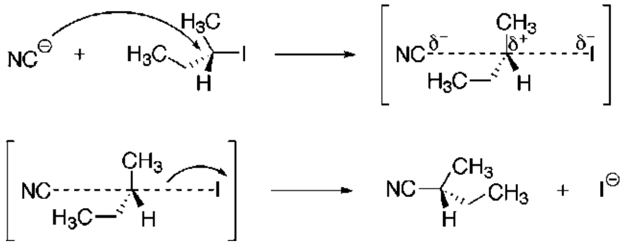
In summary, the purpose of this problem is not to solicit identification of a leaving group, but rather to induce consideration of the different reaction processes that can occur. Through such an understanding, starting materials and reaction conditions can be chosen that maximize the chances of generating a desired product with minimal side reactions.

6. *Detailed discussions focused on stereochemistry are not within the scope of this book. However, considering the products of typical S_N2 reactions, in addition to the transition state shown in Scheme 4.2, one may deduce the stereochemical course of*

this type of reaction. Predict the product of the following reaction and show the correct stereochemistry:



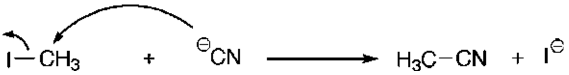
As shown below, initial reaction of a cyanide anion results in formation of the transition state shown in brackets. Release of the iodide anion results in complete inversion of the stereochemistry generating the illustrated final product.



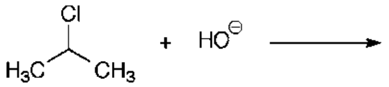
7. *Predict the products of the following reactions by pushing arrows*:

a. $I{-}CH_3 + {}^{\ominus}CN \longrightarrow$

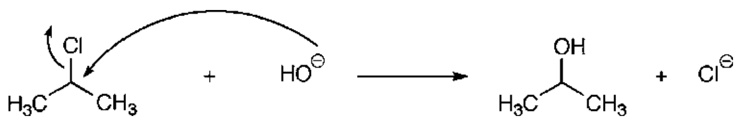
This is a direct S_N2 displacement of an iodide anion by a cyanide anion.



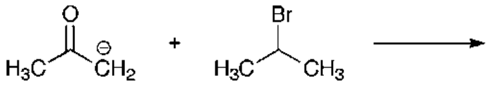
b.



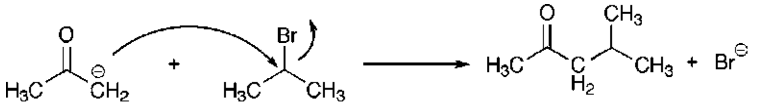
This is a direct S_N2 displacement of a chloride anion by a hydroxide anion.



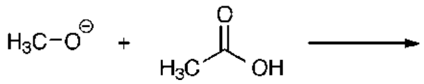
c.



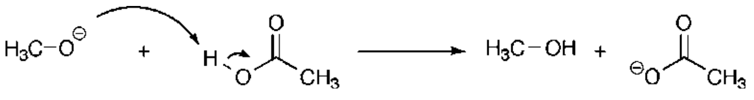
This is a direct S_N2 displacement of a bromide anion by an acyl anion.



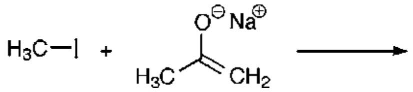
d.



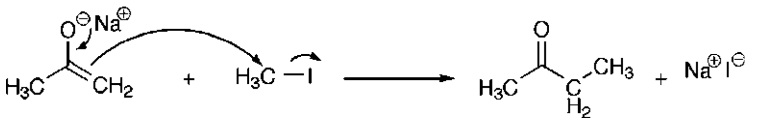
This is an acid–base proton exchange between a methoxide anion (pK_a of methanol is approximately 15) and acetic acid (pK_a = 4.75).



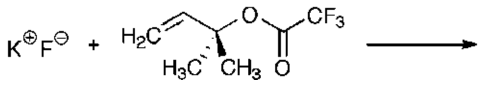
e.



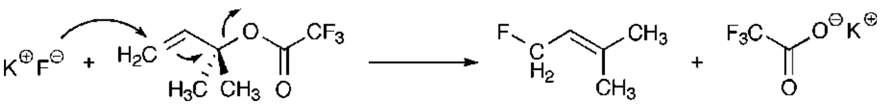
This is a direct S_N2 displacement of an iodide anion by an acyl anion. Please note that the negative charge of the acyl anion is delocalized into the carbonyl and that the negative charge is paired with a cation.



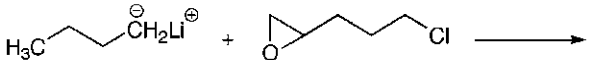
f.



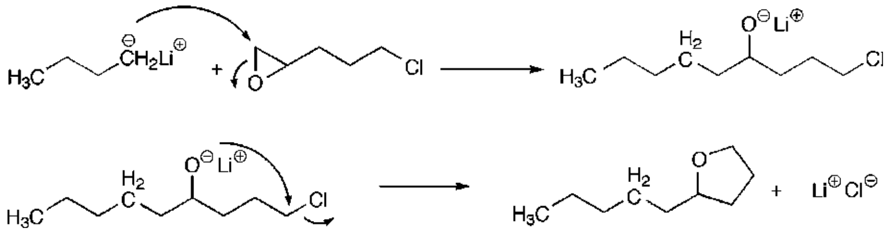
This is an S_N2' displacement of a trifluoroacetoxy anion by a fluoride anion. The related S_N2 mechanism is not favored because of steric factors. Specifically, the trifluoroacetate resides at a tertiary center. Please note that the fluoride anion is accompanied by a potassium cation and that the final trifluoroacetoxy group is presented as its potassium salt.



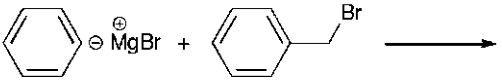
g.



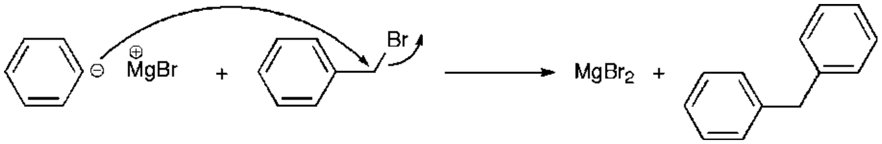
This is a two-step reaction with initial S_N2 opening of an epoxide. The opening of the epoxide is favored because of the strain associated with a three-membered ring. Subsequent S_N2 displacement of the chloride by the alkoxide resulting from epoxide opening leads to the illustrated tetrahydrofuran derivative. The purpose of this example is to illustrate that in many cases, organic reactions do not stop after an initial stage and frequently advance to generate products over several mechanistic steps.



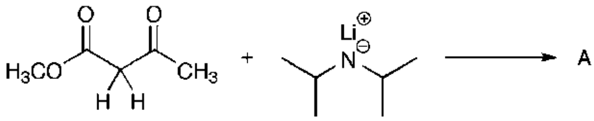
h.



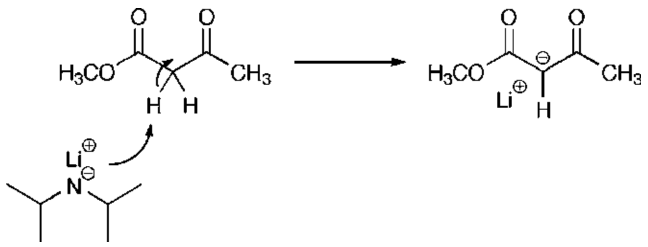
This is a direct S_N2 displacement of a bromide anion by a phenyl anion. Please note that the negative charge of the phenyl anion is accompanied by a magnesium bromide complex. This class of organic salt is known as a Grignard reagent and is characterized by the presence of magnesium and a halide such as chloride, bromide, or iodide.



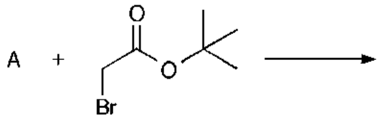
i.



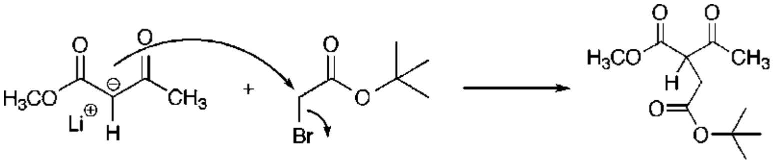
This is an acid–base proton exchange between lithium diisopropylamide (LDA, pK_a of diisopropylamine is approximately 35) and methyl acetoacetate (pK_a is approximately 12). Please note the transfer of the lithium counter ion from LDA to the deprotonated methyl acetoacetate.



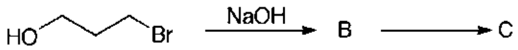
j.



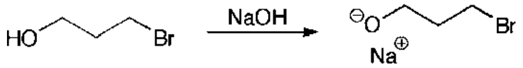
This is a direct S_N2 displacement of the bromide anion of *tert*-butyl bromoacetate by a methyl acetoacetate anion. Lithium bromide (LiBr), the salt by-product, is not shown in the reaction below.



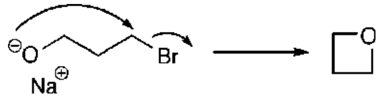
k.



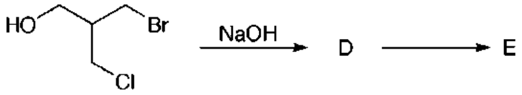
The first step of this reaction is an acid–base proton exchange between a hydroxide anion (pK_a of water is approximately 16) and a primary alcohol (pK_a is approximately 16) forming the illustrated alkoxide, **B**. Formation of water, the by-product, is not shown in this step.



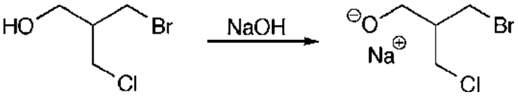
The second step of this reaction is a direct S_N2 displacement of a bromide anion by the alkoxide anion present in the same molecule. This step leads to formation of oxetane, **C**. Formation of sodium bromide (NaBr), the salt by-product of this step, is not shown.



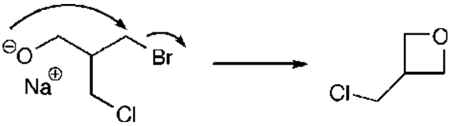
l.



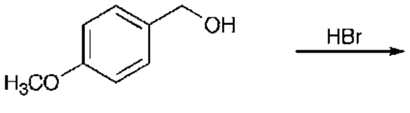
The first step of this reaction is an acid–base proton exchange between a hydroxide anion (pK_a of water is approximately 16) and a primary alcohol (pK_a is approximately 16) forming the illustrated alkoxide, **D**. Formation of water, the by-product, is not shown in this step.



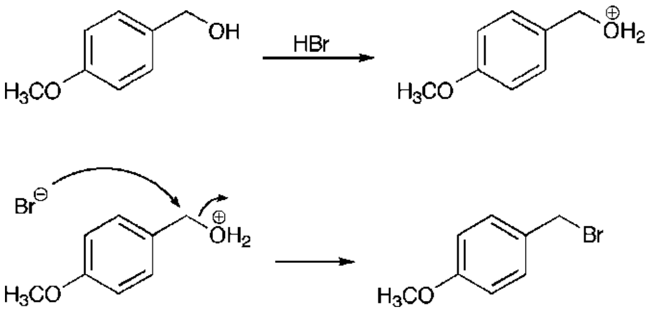
The second step of this reaction is a direct S_N2 displacement of a bromide anion by the alkoxide anion present in the same molecule. This step leads to formation of the oxetane, **E**. Please note that displacement of the bromide is preferred over displacement of the chloride because bromide is a better leaving group than chloride. Formation of sodium bromide (NaBr), the salt by-product of this step, is not shown.



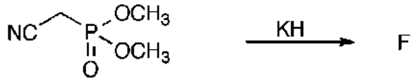
m.



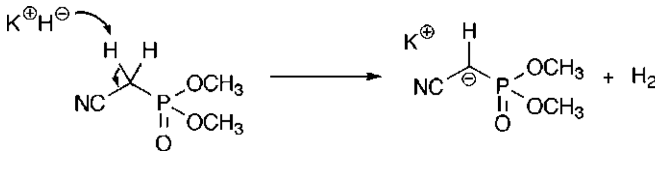
This is a solvolysis reaction that proceeds in two steps. The first step involved protonation of the hydroxy group of *p*-methoxybenzyl alcohol. Once protonated, a bromide ion displaces water, generating the illustrated product. The reaction shown below demonstrates this reaction through an S_N2 mechanism; however, this reaction can also be represented through an S_N1 reaction involving initial dissociation of water followed by reaction of the resulting cation with a bromide anion.



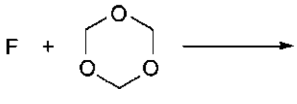
n.



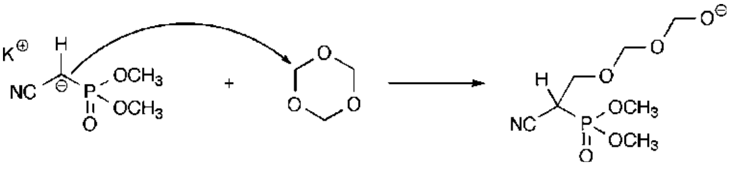
Potassium hydride (KH) is a reactive base possessing a potassium cation and a hydrogen anion (hydride ion). The hydride ion reacts as any other base mentioned thus far and extracts acidic protons generating hydrogen gas and leaving behind anions with associated potassium cations. In this case, the dimethyl cyanomethylphosphonate anion, **F**, is formed.



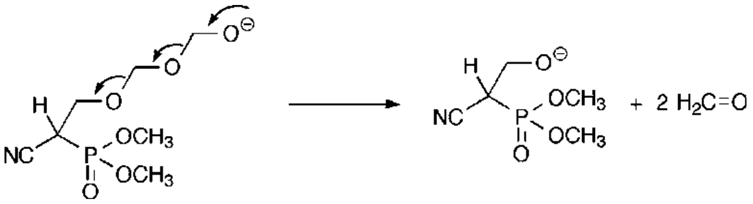
o.



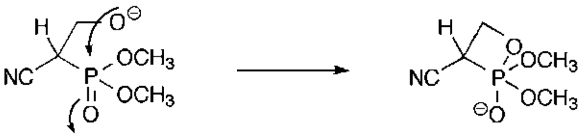
At first glance, this reaction appears simple with the phosphonate anion illustrated in Problem 7(n) displacing an alkoxide anion from trioxane as illustrated below.



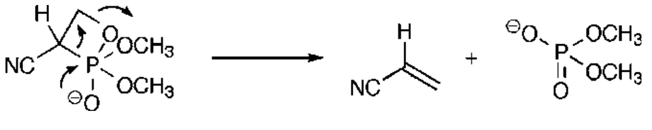
However, as continually alluded to, anions, once formed, can participate in further reactions. Trioxane is essentially a trimer of formaldehyde ($H_2C{=}O$) and is more stable and easier to handle than its monomeric form. When an anion opens the trioxane ring, the resulting anion degrades, as shown below, with release of two equivalents of formaldehyde. The resulting species is essentially that resulting from reaction of the initial phosphonate anion with formaldehyde itself. Please note the net incorporation of only one carbon atom and only one oxygen atom. Additionally, the potassium cation is omitted from the remainder of the illustrations for clarity.



Again, referring to the ability of anions to undergo further transformations, we must recognize that phosphorus is a unique element with a strong affinity for oxygen. Furthermore, the phosphorus–oxygen double bond bears much of the same reactivity of a carbon–oxygen double bond and will accept addition of a nucleophile into the system as shown below. The illustrated four-membered species is known as a phosphetane.



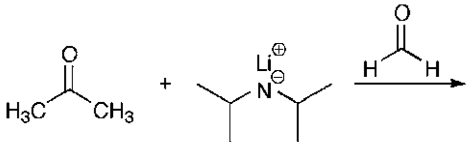
As phosphorus exhibits a strong affinity for oxygen, phosphetane rings are known to undergo further reactions. As illustrated below, the negative charge on the oxygen is capable of breaking the adjacent carbon–phosphorus bond and transferring the negative charge to the carbon atom. Carrying this cycle forward, the negatively charged carbon atom participates in an E2 elimination (Chapter 6) with formation of a new double bond and cleavage of the adjacent carbon–oxygen bond. The resulting two species are an olefin and a phosphate anion.



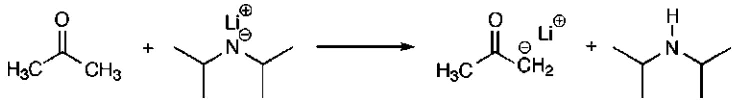
This reaction, known as a Horner–Emmons olefination, was presented to illustrate that through consideration of the electronic nature of a given starting material and the transient species involved in reactions with this material, products of more complex reactions may be identified. However, it is important to note that while this sequence appears complex, each step involved utilizes principles of arrow pushing easily applied from material presented in this book.

8. *Addition reactions and conjugate addition reactions, to be discussed in Chapter 7, are related to* S_N2 *and* S_N2' *reactions, respectively. We can make these comparisons if we recognize that the carbonyl double bond contains a leaving group. Specifically, if a nucleophile adds to the carbon of a carbonyl, the carbonyl double bond becomes a carbon–oxygen single bond with a negative charge residing on the oxygen. Additionally, the trigonal-planar geometry of the carbonyl carbon is converted to tetrahedral geometry. With these points in mind, predict the products of the following reactions and explain your answers. For Problem 8(b), the nucleophile is a methyl anion associated with the illustrated cuprate.*

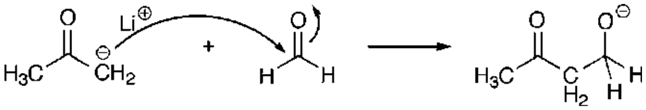
a.



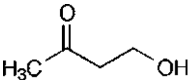
The first stage of this reaction is deprotonation of acetone by LDA in a manner analogous to that demonstrated in Problem 7(i).



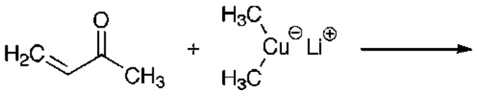
The second stage of the reaction is addition of the acetone anion to formaldehyde as shown below.



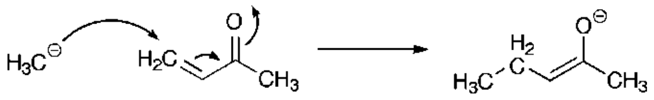
Protonation of the resulting alkoxide anion leads to the alcohol illustrated below. This reaction is known as an aldol condensation.



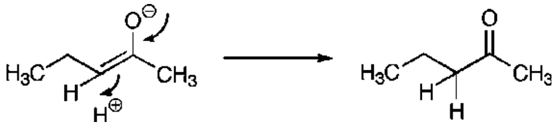
b.



The copper-based reagent shown in the above reaction is known as a cuprate. This specific compound is dimethyl lithiocuprate and is an excellent carrier of methyl anions. Cuprates are unique in their ability to preferentially deliver nucleophiles to carbonyl groups through adjacent double bonds and in manners analogous to S_N2' mechanisms. Thus, as illustrated below, arrow pushing demonstrates how cuprates add nucleophiles to unsaturated carbonyl systems.

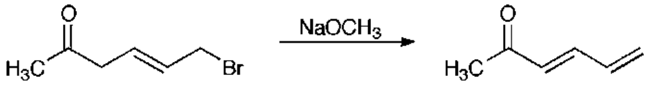


When the illustrated anion is treated with acid, proton transfer generates the final product as shown below.

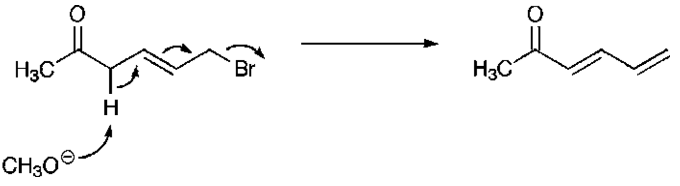


9. *Propose a reasonable mechanism for each of the following reactions. Explain your answers by pushing arrows.*

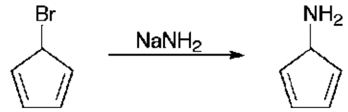
a.



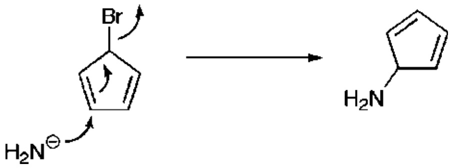
This reaction proceeds through initial deprotonation adjacent to the ketone followed by an S_N2'-type movement of electrons through the double bond and elimination of a bromide ion.



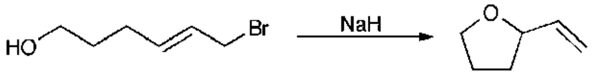
b.



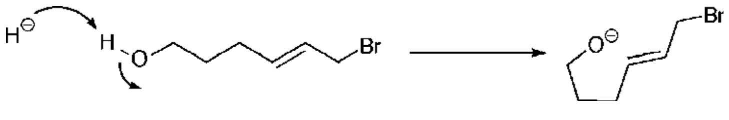
This reaction is an S_N2' displacement of a bromide anion.



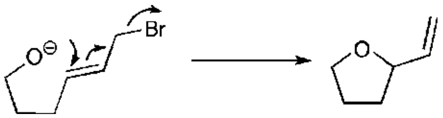
c.



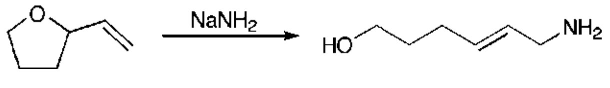
The first step of this reaction is deprotonation of the alcohol with sodium hydride.



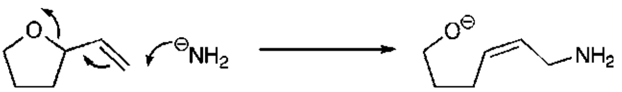
The second step of this reaction is an intramolecular S_N2' reaction with the alkoxide anion displacing the bromide anion through the double bond.



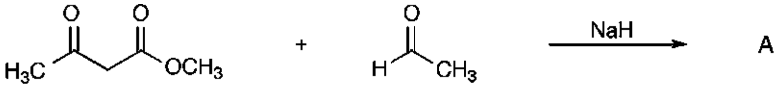
d.

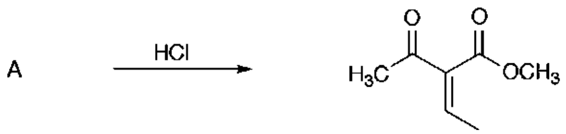


This reaction is an S_N2' displacement of an alkoxide anion through the double bond.

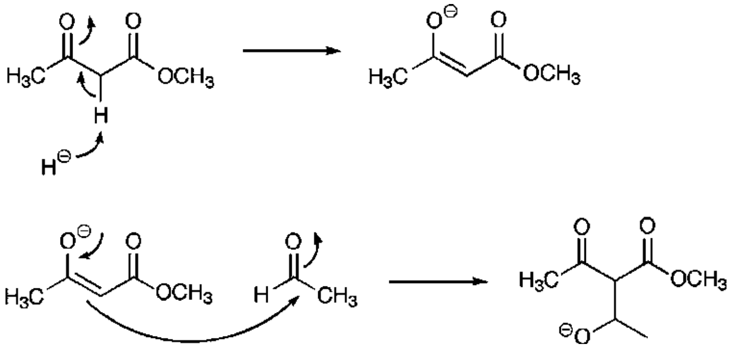


10. α,β-*unsaturated carbonyls are readily formed from the corresponding* β-*hydroxy ketones. Explain the product of the following reaction*:

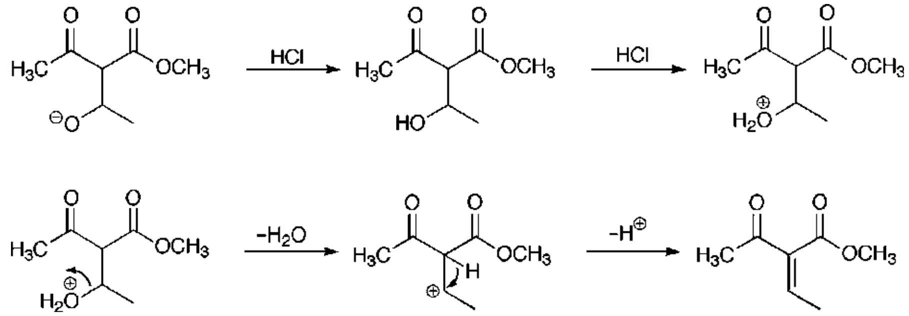




Upon examining the reaction, the initial phase of this sequence can be defined as an aldol condensation [see Problem 8(a)]. Under the specified conditions, hydride is used to deprotonate methyl acetoacetate and the resulting anion adds to the acetaldehyde carbonyl giving the aldol product, **A**.



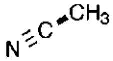
Treating the aldol adduct, **A**, with hydrochloric acid protonates the alkoxide anion and then protonates the resulting alcohol as part of a solvolysis reaction. Water then leaves, generating a carbocation. The carbocation then undergoes an E1 elimination (see Chapter 6) giving the illustrated product.



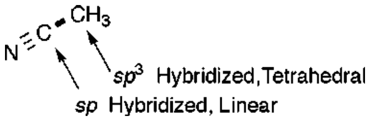
CHAPTER 5 SOLUTIONS

1. *For the following molecules, state the hybridization (*sp, sp^2, sp^3*) of the orbitals associated with the highlighted bond. Also, state the geometry of the bound atomic centers (linear, bent, trigonal planar, tetrahedral).*

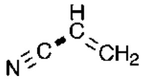
a.



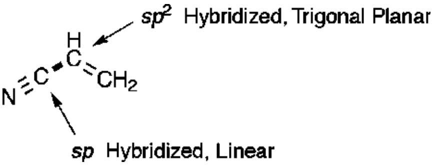
The highlighted bond joins a nitrile carbon atom to a methyl carbon atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. However, the methyl carbon is joined to the nitrile carbon and three hydrogen atoms. Therefore, because the methyl carbon is bound to four separate atoms, this carbon is sp^3 hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the methyl carbon is connected to its bound atoms in a tetrahedral geometry.



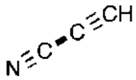
b.



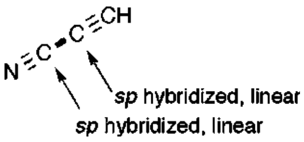
The highlighted bond joins a nitrile carbon atom to a vinyl carbon atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. However, the vinyl carbon is joined to the nitrile carbon, a hydrogen atom, and a second vinyl carbon atom. Because the two vinyl carbon atoms are joined by a double bond, there can be no more than three atoms bound to the highlighted vinyl carbon. Therefore, because the vinyl carbon is bound to three separate atoms, this carbon is sp^2 hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the vinyl carbon is connected to its bound atoms in a trigonal planar geometry.



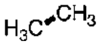
c.



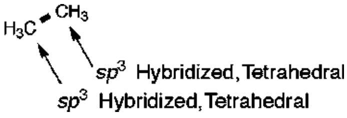
The highlighted bond joins a nitrile carbon atom to an alkyne carbon atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. Additionally, the alkyne carbon is joined to the nitrile carbon and a second alkyne carbon atom. Because the two alkyne carbon atoms are joined by a triple bond, there can be no more than two atoms bound to the highlighted alkyne carbon. Therefore, because the alkyne carbon is bound to two separate atoms, this carbon is *sp* hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the alkyne carbon is connected to its bound atoms in a linear geometry.



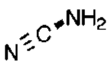
d.



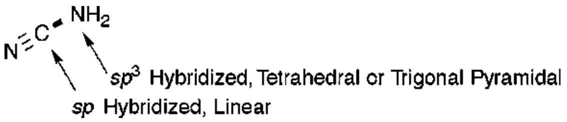
The highlighted bond joins two methyl carbon atoms. Each methyl carbon is joined to a methyl carbon and three hydrogen atoms. Therefore, because each methyl carbon is bound to four separate atoms, they are sp^3 hybridized. Based on the atomic hybridizations, each methyl carbon is connected to its bound atoms in tetrahedral geometries.



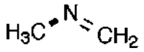
e.



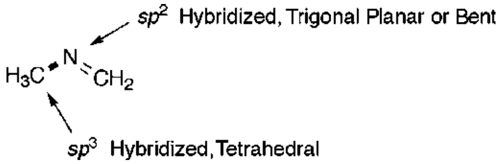
The highlighted bond joins a nitrile carbon atom to an amine nitrogen atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. However, the amine nitrogen is joined to the nitrile carbon and two hydrogen atoms. Additionally, the amine nitrogen possesses one lone electron pair. Therefore, because the amine nitrogen is bound to three separate atoms and possesses one lone electron pair, this nitrogen is sp^3 hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the amine nitrogen is connected to its bound atoms and lone electron pair in a tetrahedral geometry. Please note that because the nitrogen is only bound to three atoms, the tetrahedral relationship between the bound atoms and lone electron pair can also be referred to as trigonal pyramidal (not considering the contributions of the lone electron pair to the geometry) because the geometry represents a three-sided pyramid.



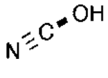
f.



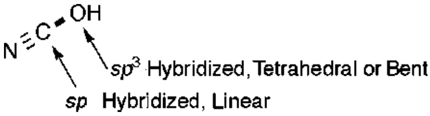
The highlighted bond joins a methyl carbon atom to an imine nitrogen atom. The methyl carbon atom, being joined to three hydrogen atoms and an imine nitrogen atom, is bound to four separate atoms and is, therefore, sp^3 hybridized. The imine nitrogen atom is bound to a methyl carbon atom through a single bond and to a second carbon atom through a double bond. Additionally, the imine nitrogen possesses one lone electron pair. Therefore, because the imine nitrogen is bound to two separate atoms and possesses one lone electron pair, this nitrogen is sp^2 hybridized. Based on the atomic hybridizations, the methyl carbon is connected to its bound atoms in a tetrahedral geometry, and the imine nitrogen is connected to its bound atoms and lone electron pair in a trigonal planar geometry. Please note that the molecular structure is referred to as bent.

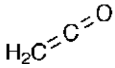


g.



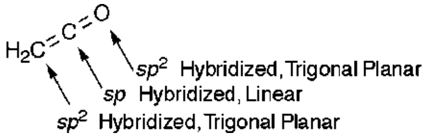
The highlighted bond joins a nitrile carbon atom to a hydroxy oxygen atom. The nitrile carbon atom, being joined to a nitrogen atom via a carbon–nitrogen triple bond, can only be joined to one additional atom. Therefore, this atom is *sp* hybridized. However, the hydroxy oxygen is joined to the nitrile carbon and one hydrogen atom. Additionally, the hydroxy oxygen possesses two lone electron pairs. Therefore, because the hydroxy oxygen is bound to two separate atoms and possesses two lone electron pairs, this oxygen is sp^3 hybridized. Based on the atomic hybridizations, the nitrile carbon is connected to its bound atoms in a linear geometry, and the hydroxy oxygen is connected to its bound atoms and lone electron pairs in a tetrahedral geometry. Please note that the molecular structure is referred to as bent at the oxygen atom.

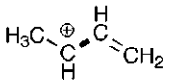


h. 

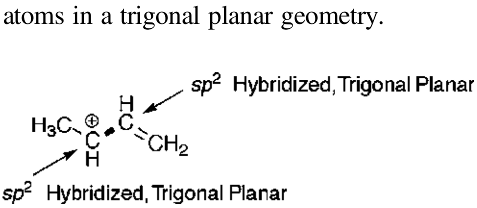
(Answer for both double bonds.)

For this compound, the CH_2 carbon is bound to the central carbon through a double bond. Furthermore, this carbon atom is bound to two hydrogen atoms. Because this carbon atom is bound to only three atoms, it is sp^2 hybridized. However, the central carbon atom, being bound to the CH_2 carbon atom through a double bond, is bound to an oxygen atom through a double bond. Thus, the central carbon atom is bound to only two atoms and is sp hybridized. Finally, the oxygen atom is bound to the central atom through a double bond. Additionally, the oxygen atom possesses two lone electron pairs. Because the oxygen atom is bound to only one atom and possesses two lone electron pairs, it is sp^2 hybridized. Regarding geometry, the CH_2 carbon, being bound to three atoms, is trigonal planar. Furthermore, the central carbon, being bound to two atoms, is linear. Lastly, the oxygen atom, being bound to only one atom and possessing two lone electron pairs, is trigonal planar.

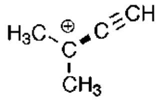


i. 

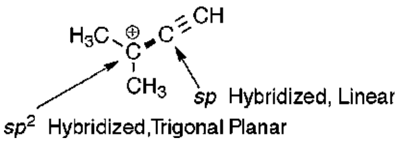
For this compound, the positively charged CH carbon is bound to a vinyl carbon, a methyl carbon, and a hydrogen through single bonds. Because this carbon atom is bound to only three atoms, it is sp^2 hybridized. Additionally, the vinyl carbon atom is bound to the positively charged carbon atom, a hydrogen and a second vinyl carbon. Because the two vinyl carbon atoms are joined by a double bond, there can be no more than three atoms bound to the highlighted vinyl carbon. Therefore, because the vinyl carbon is bound to three separate atoms, this carbon is sp^2 hybridized. Based on the atomic hybridizations, the positively charged carbon is connected to its bound atoms in a trigonal planar geometry. Likewise, the vinyl carbon is connected to its bound atoms in a trigonal planar geometry.



j.

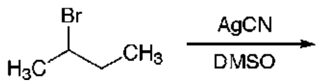


For this compound, the positively charged carbon is bound to an alkyne carbon and two methyl carbons through single bonds. Because this carbon atom is bound to only three atoms, it is sp^2 hybridized. Additionally, the alkyne carbon atom is bound to the positively charged carbon atom and a second alkyne carbon atom. Because the two alkyne carbon atoms are joined by a triple bond, there can be no more than two atoms bound to the highlighted alkyne carbon. Therefore, because the alkyne carbon is bound to two separate atoms, this carbon is *sp* hybridized. Based on the atomic hybridizations, the positively charged carbon is connected to its bound atoms in a trigonal planar geometry, and the alkyne carbon is connected to its bound atoms in a linear geometry.

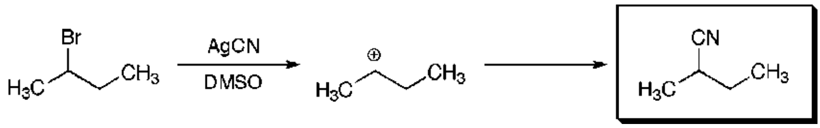


2. *Predict all of the products of the following reactions:*

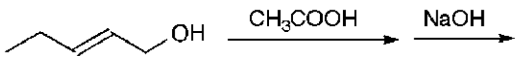
a.



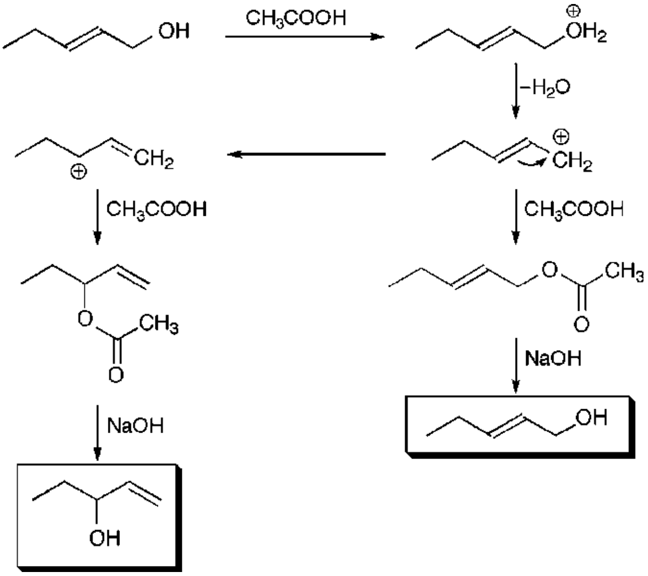
Silver is very efficient at removing halides, resulting in generation of carbocations. Because, once a carbocation is formed, a 1,2-hydride shift applied to the illustrated secondary carbocation can only generate a less stable primary carbocation or an identical secondary carbocation, therefore, there is only one product formed in this reaction.



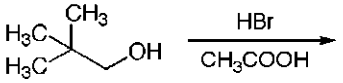
b.



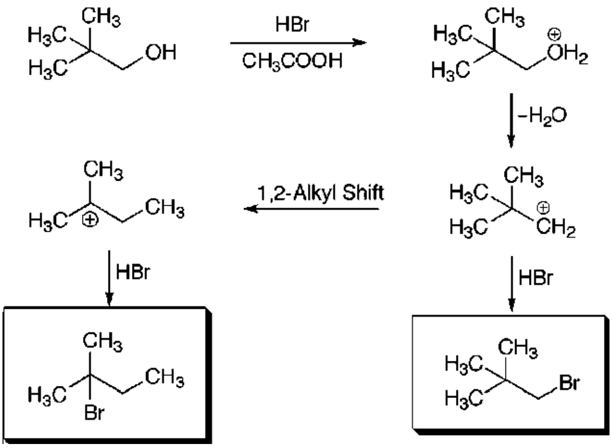
This is a solvolysis reaction where the alcohol is protonated and water leaves, generating a carbocation. The resulting carbocation then joins with acetic acid or migrates through the double bond (note the arrow pushing). The migrated carbocation then joins with acetic acid. In both cases, the resulting acetates are cleaved with sodium hydroxide generating a mixture of two alcohols—regenerated starting material and 3-hydroxy-1-pentene.



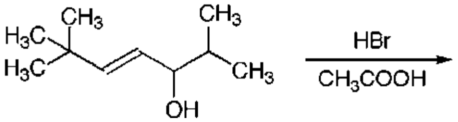
c.



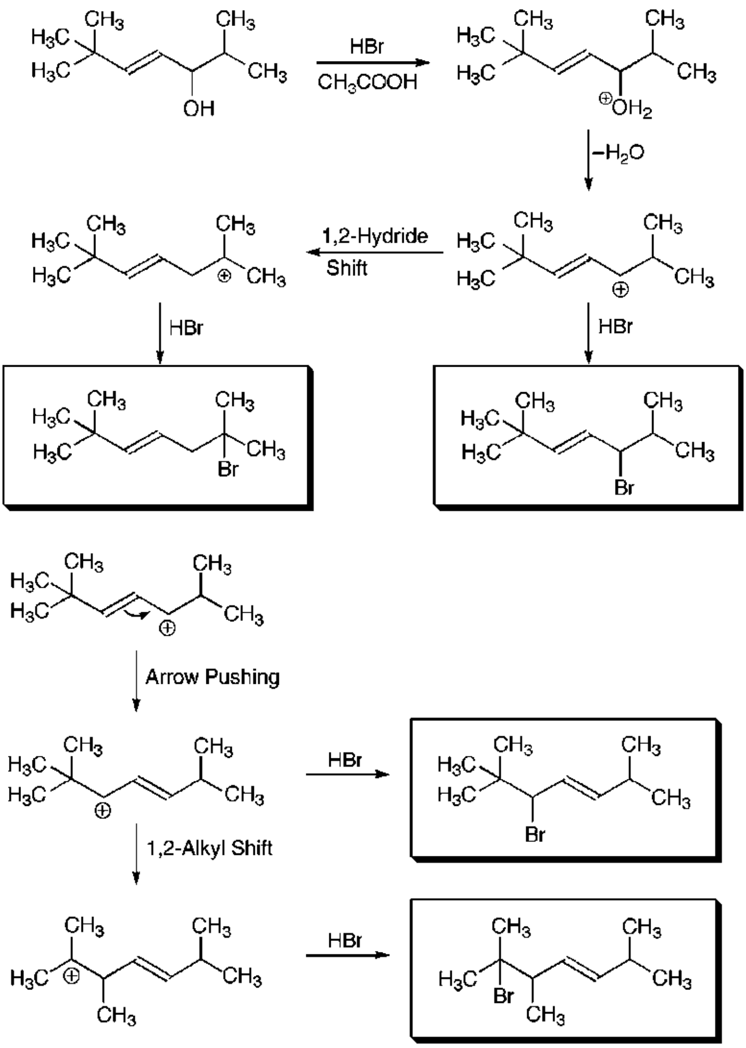
Like the previous example, this is a solvolysis reaction. Initial protonation of the alcohol followed by water leaving generates a primary carbocation. The bromide can then add to this carbocation generating neopentyl bromide. Since, for this carbocation, 1,2-hydride shifts cannot occur, a 1,2-alkyl shift generates a more stable tertiary carbocation. This new carbocation is not subject to possible 1,2-hydride shifts because any such transformation would generate either a less stable secondary carbocation or a less stable primary carbocation. When bromide adds to the tertiary carbocation, a second alkyl bromide is formed.



d.

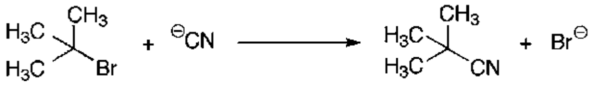


Like Problems 2(b) and 2(c), this is also a solvolysis reaction. However, due to the increased complexity of the starting compound, the potential product mixture is more complex. Specifically, if we consider the initial solvolysis step and elimination of water, we notice that an allyl carbocation is formed that is adjacent to a migratable hydrogen atom. While reaction of this carbocation with bromide generates a secondary allyl bromide, a 1,2-hydride shift followed by reaction with bromide generates a tertiary bromide. Alternatively, if the positive charge migrates through the double bond (see arrow pushing), an allylic carbocation adjacent to a *tert*-butyl group results. Reaction of this carbocation with bromide generates a new allyl bromide. However, if a 1,2-alkyl shift occurs, the resulting tertiary carbocation can react with bromide to form a new tertiary bromide.



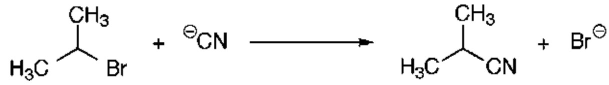
3. *For each of the following reactions, determine which will proceed via an* S_N1 *or an* S_N2 *mechanism. In cases where both may be applicable, list appropriate reaction conditions (e.g., solvents, reagents) that would favor* S_N1 *over* S_N2 *and vice versa. Explain your answers.*

a.



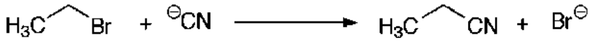
Because tertiary centers are not susceptible to S_N2 reactions, this reaction will proceed via an S_N1 mechanism.

b.



This reaction will show competition between S_N1 and S_N2 mechanisms due to the fact that this center is less hindered than a tertiary center but more hindered than a primary center. An S_N1 mechanism will be favored using highly polar, aprotic solvents to stabilize the forming carbocation. An S_N2 mechanism will be favored when nonpolar solvents are used.

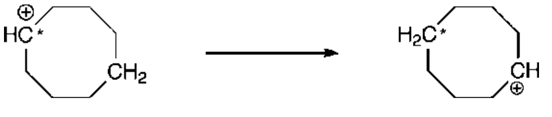
c.



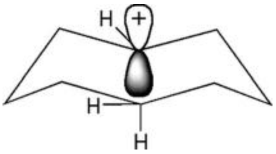
This reaction will proceed through an S_N2 mechanism. In general, primary centers are not sterically encumbered enough to inhibit S_N2 reactions. Additionally, recall that primary carbocations are much less stable than tertiary carbocations, making an S_N1 mechanism highly unlikely for this transformation.

4. *In studying 1,2-alkyl and hydride shifts, we explored the observation that shifts will not occur unless the newly formed carbocation is more stable than the starting carbocation. Additionally, as illustrated in Figure 5.12, these shifts were explained using hyperconjugation, thus requiring that the orbital containing the positive charge and the bond containing the shifting group lie within the same plane. This is necessary in order to allow sufficient orbital overlap for the shift to take place.*

In addition to 1,2-shifts, which occur between adjacent bonds, other shifts are possible where the migrating group apparently moves across space. As with 1,2-shifts, these additional shifts can only occur when the positively charged empty p *orbital lies within the same plane as the bond containing the migrating group, thus allowing sufficient orbital overlap. With this in mind, explain the following 1,5-hydride shift. (Hint: Consider different structural conformations. You may want to use models.) Asterisk (*) marks enrichment with ^{13}C.*



If the eight-membered ring is drawn as illustrated below, a planar relationship can be found between the empty *p* orbital and a carbon–hydrogen bond on the opposite side of the ring. If the hydrogen atom is located on a carbon atom designated 1, by numbering the carbon atoms around the ring, the positive charge is localized on carbon atom 5. Thus, the established relationship between a hydrogen atom on carbon 1 and a positive charge on carbon 5 allows recognition that a 1,5-hydride shift can occur and is required to explain the described transformation.



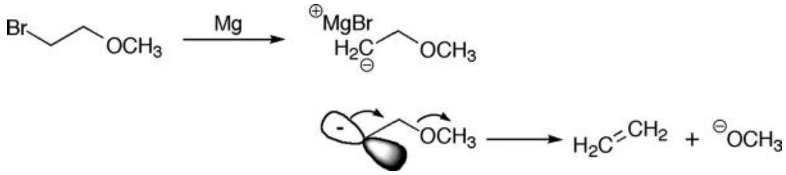
CHAPTER 6 SOLUTIONS

1. *E2 eliminations do not necessarily require acidic protons in order to proceed. Explain how this can occur.*

   The orientation of any proton in a *trans*-periplanar relationship to a given leaving group is usually enough to allow elimination to occur under basic conditions even when, in the absence of an electron-withdrawing group, the proton is not acidic enough to be removed.

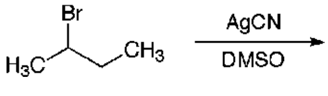
2. *When* $CH_3OCH_2CH_2CH_2Br$ *is treated with magnesium, we get the Grignard reagent* $CH_3OCH_2CH_2CH_2MgBr$. *However, when* $CH_3OCH_2CH_2Br$ *is treated with magnesium, the product isolated is* $H_2C{=}CH_2$. *Explain this result.*

   Grignard reagents are carbanions stabilized by a MgBr cation. As with all anionic species, if a leaving group is situated on an adjacent center, the structure is subject to an E2 elimination process. Furthermore, CH_3O^- is a sufficient leaving group when it is located adjacent to an anionic center. Therefore, in the case of bromomethoxyethane, E2 elimination leads to formation of ethylene when the negative charge adopts a *trans*-periplanar relationship to the methoxy group.



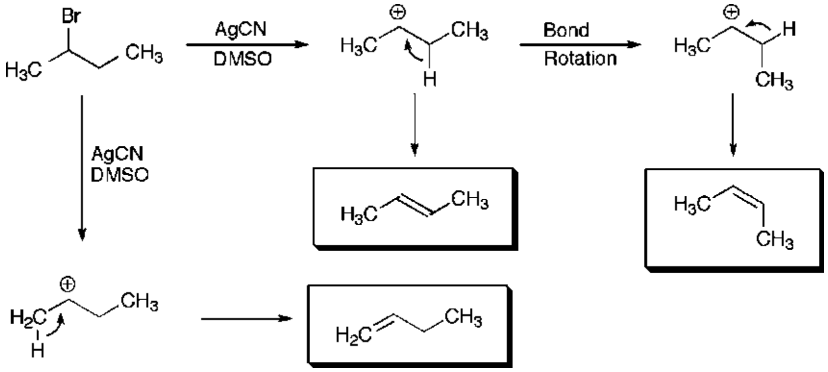
3. *With an understanding of E1 mechanisms, one may realize that under S_N1 reaction conditions multiple products may form. In addition to the products predicted in Chapter 5 for the following molecules, predict plausible elimination products.*

a.

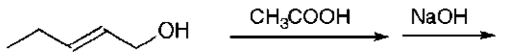


Silver is very efficient at removing halides, resulting in generation of carbocations. Because protons adjacent to carbocations are acidic and, therefore, participate in

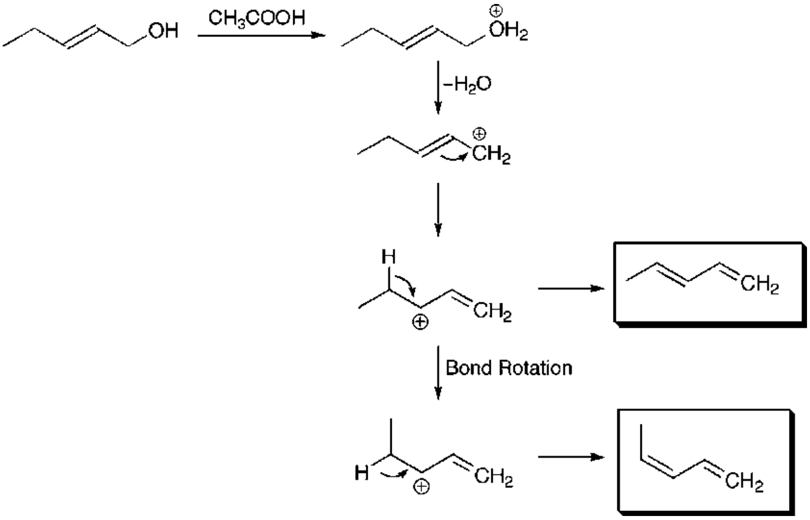
E1 elimination reactions, several potential products can be identified. These are illustrated below using arrow pushing.



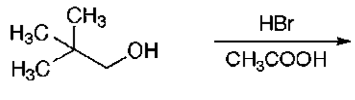
b.



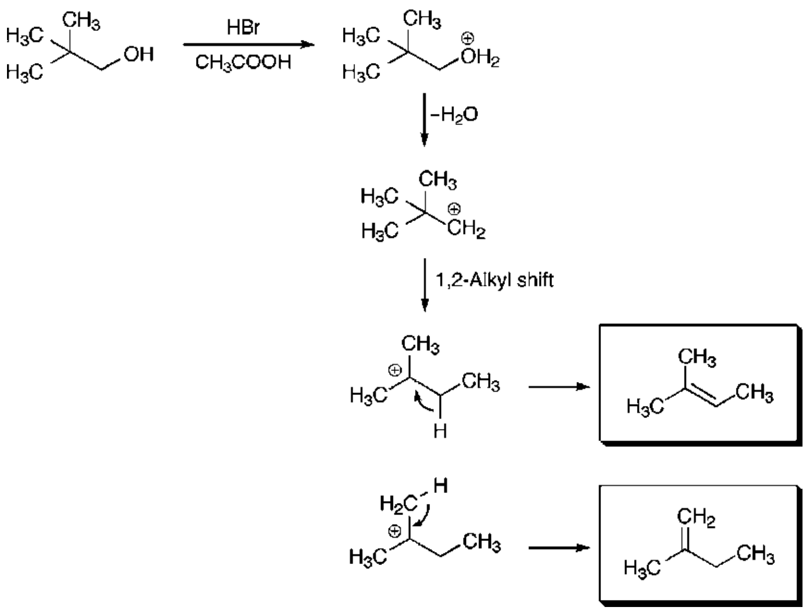
This is a solvolysis reaction where the alcohol is protonated and water leaves, generating a carbocation. Because protons adjacent to carbocations are acidic and, therefore, participate in E1 elimination reactions, several potential products can be identified. These are illustrated below using arrow pushing.



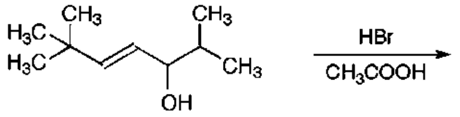
c.



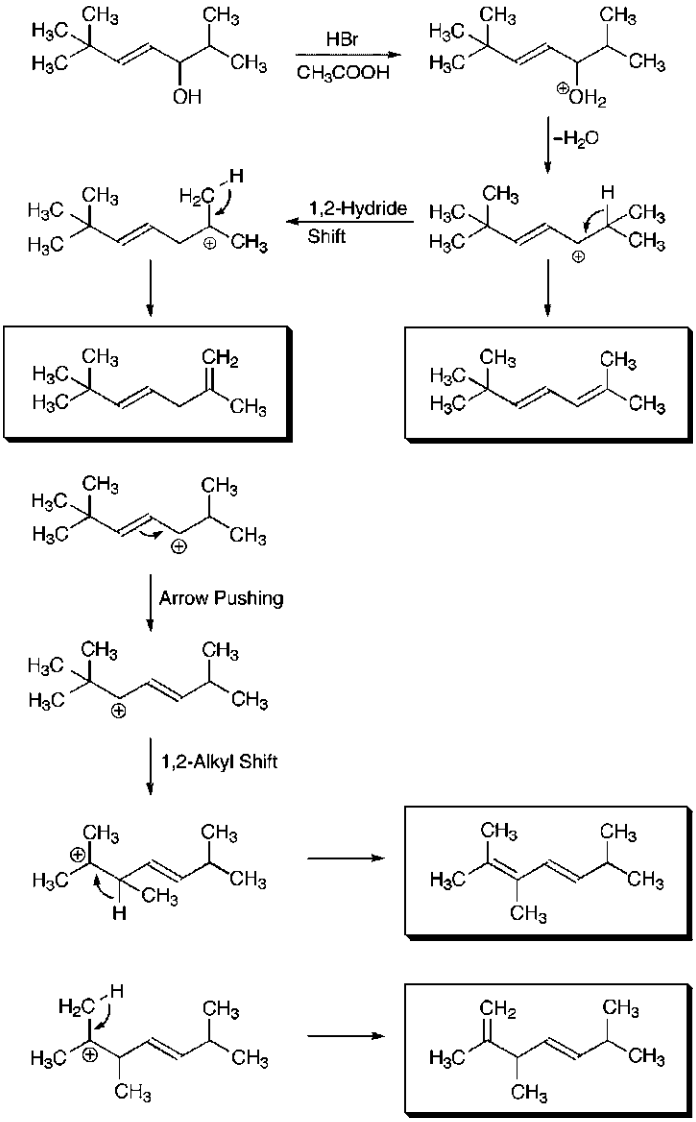
Like the previous example, this is a solvolysis reaction. Initial protonation of the alcohol followed by water leaving generates a primary carbocation. Since, for this carbocation, there are no protons adjacent to the carbocation, no direct E1 elimination products can form. However, if a 1,2-alkyl shift occurs, the resulting tertiary carbocation can participate in such reactions. Potential E1 elimination products are illustrated below using arrow pushing.



d.



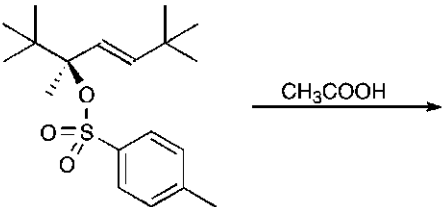
Like Problems 3(b) and 3(c), this is a solvolysis reaction. However, due to the increased complexity of the starting compound, the potential product mixture is more complex. Specifically, if we consider the initial solvolysis step and elimination of water, we notice that an allyl carbocation is formed that is adjacent to a migratable hydrogen atom. While this carbocation can undergo an E1 elimination reaction, a 1,2-hydride shift generates a new carbocation that is also capable of E1 forming E1 elimination products. Furthermore, if the positive charge migrates through the double bond (see arrow pushing), an allylic carbocation adjacent to a *tert*-butyl group results. While this new carbocation bears no adjacent hydrogen atoms, a 1,2-alkyl shift generates a new carbocation that does possess adjacent protons. This new carbocation can liberate E1 elimination products. All potential E1 elimination products are illustrated below using arrow pushing.



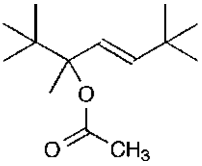
Please note: The most stable products possess conjugated double bonds.

4. *Presently, several different organic reaction mechanisms have been presented. Keeping all of these in mind, predict all of the possible products of the following reactions and list the mechanistic type or types from which these products result.*

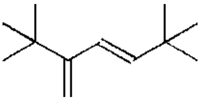
a.



Following initial solvolysis of the tosylate, addition of acetic acid to the carbocation generates an S_N1 product. Please note that there is no preservation of the stereochemical configuration in this reaction.

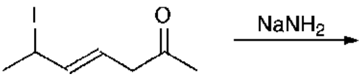


E1 elimination applied to the carbocation formed during solvolysis liberates an olefin.

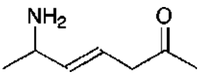


Please note: Since the carbocation formed during solvolysis is both tertiary and allylic, it is very stable and migration reactions are not likely to occur.

b.

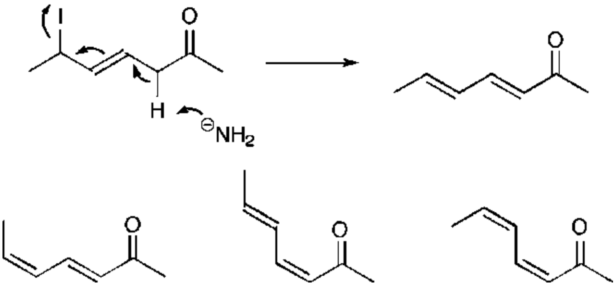


S_N2 displacement of the iodide generates an allylic amine.

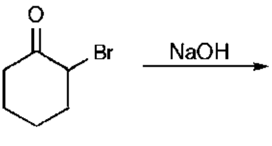


S_N2' displacement of the iodide generates a mixture of two allylic amines with the amine placed on the opposite side of the double bond.

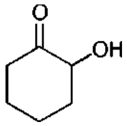
E2 elimination resulting from removal of a proton adjacent to the carbonyl liberates a diene. Please note that, depending upon the spatial relationship between the carbonyl and the double bond, additional illustrated dienes can form.



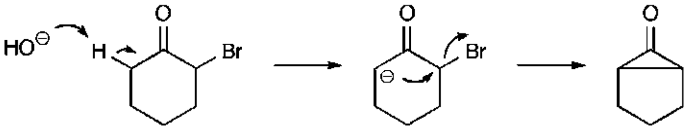
c.



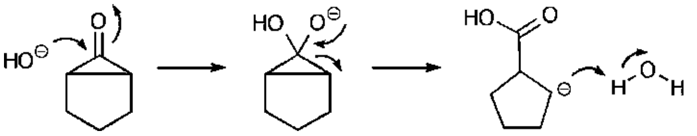
Direct S_N2 displacement of the bromide would be expected to liberate the illustrated hydroxyketone.



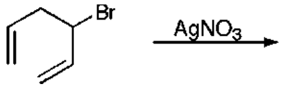
However, this is a special case reaction known as the Favorskii rearrangement. As illustrated below using arrow pushing, sodium hydroxide extracts a proton adjacent to the ketone, and the resulting anion displaces the bromide ion, generating a new three-membered ring.



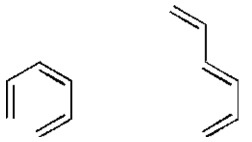
As alluded to in previous discussions, carbonyl groups are polarized with a partial positive charge residing on the carbon atom and a partial negative charge residing on the oxygen atom. This polarization has been used in discussions of charge delocalization. As will be addressed in the next chapter, the polarized nature of carbonyls render them good electrophiles and, as such, capable of accepting nucleophiles at the partial positive center. As illustrated below, a hydroxide anion can now add to the carbonyl, placing a negative charge on the original carbonyl oxygen. That negative charge can then return to the original carbonyl carbon atom and open the three-membered ring, relieving strain and forming a cyclopentane carboxylic acid.



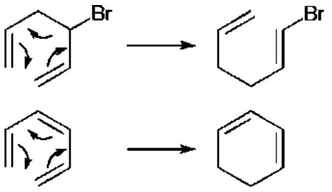
d.



As previously mentioned (see Problem 3(a)), silver cations are very efficient at removing halide anions. Therefore, under these conditions, liberation of an allylic cation is favorable. This cation can then generate the E1 elimination products shown. Please note that these products are dependent upon the relationship between the two terminal double bonds.

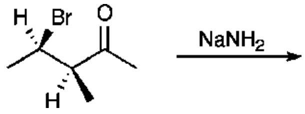


Additionally, as mentioned in Chapter 1, concerted reaction mechanisms can be described using arrow pushing. As illustrated below, both the starting bromide and one of the trienes can undergo Cope rearrangements to form new products. While these reactions are not within the scope of this book, it is important to recognize these reactions. For more detailed information, readers are referred to their introductory organic chemistry textbooks.

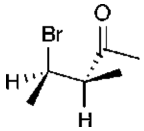


5. *As mentioned earlier, stereochemistry is not of great concern in this book. However, certain mechanistic types will show specific stereochemical consequences when*

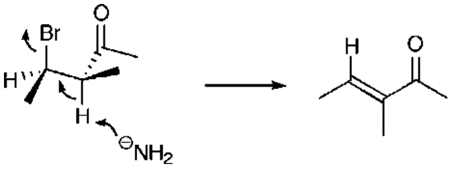
acting on chiral molecules. With this in mind, predict the product resulting from the E2 elimination of HBr when the illustrated isomer of 4-bromo-3-methyl-2-pentanone is treated with sodamide. Show all stereochemistry and explain your answer.



In order to approach this problem, we must first identify the structure of the starting compound when the acidic proton is oriented *trans*-periplanar to the bromide. The relevant configuration is illustrated below and can be visualized using molecular models.

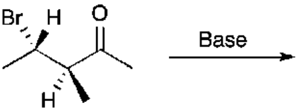


Realizing that the two methyl groups are oriented as projecting out of the same side of the molecule, E2 elimination of HBr can only form a product with the methyl groups *cis* to one another. The formation of this product is illustrated below using arrow pushing.

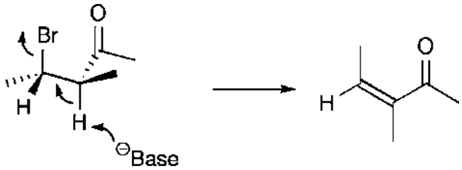


6. *Based on the answer to Problem 5, predict the product of the following reactions and show all stereochemistry*:

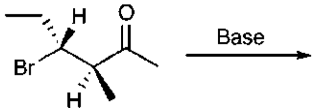
a.



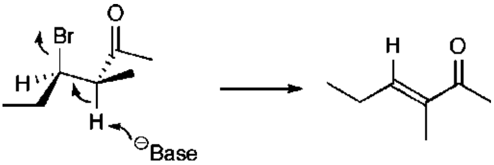
Aligning the acidic proton with the bromide in a *trans*-periplanar orientation allows formation of the illustrated product as shown using arrow pushing.



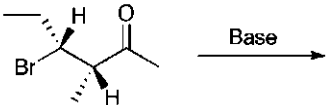
b.



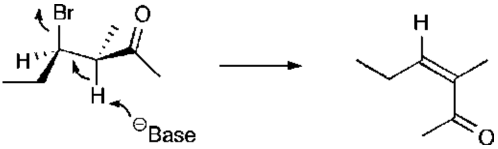
Aligning the acidic proton with the bromide in a *trans*-periplanar orientation allows formation of the illustrated product as shown using arrow pushing.



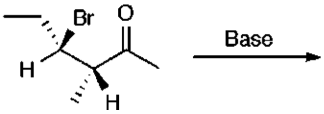
c.



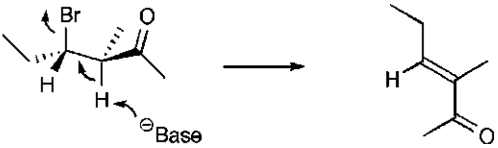
Aligning the acidic proton with the bromide in a *trans*-periplanar orientation allows formation of the illustrated product as shown using arrow pushing.



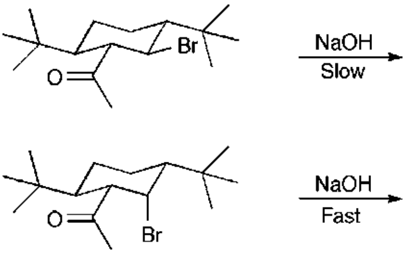
d.



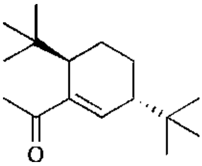
Aligning the acidic proton with the bromide in a *trans*-periplanar orientation allows formation of the illustrated product as shown using arrow pushing.



7. *Explain the results of the following experiment*:

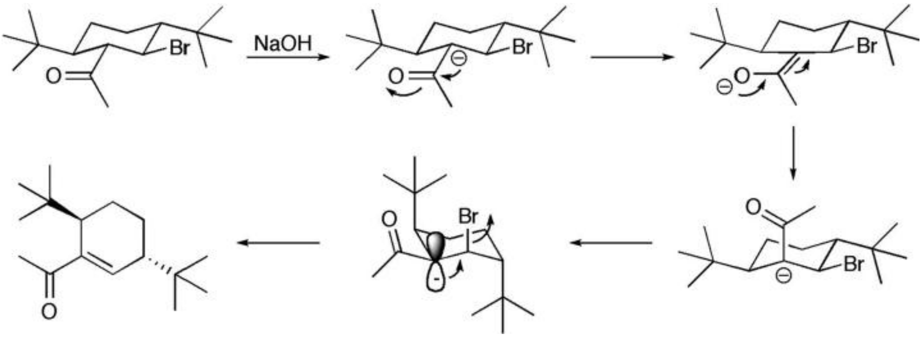


The product for both of these reactions is the cyclohexene shown below.



This product forms via an E2 elimination mechanism. Consequently, the elimination reaction is only favored if a *trans*-periplanar relationship exists between the acidic proton and the bromide. In the case of the starting material used in the "fast" reaction, this is the case. However, looking at the starting material used in the "slow" reaction, no *trans*-periplanar relationship exists between the acidic proton and the bromide.

Because the slow reaction does, in fact, form the same product as that formed in the fast reaction, transformations allowing a *trans*-periplanar arrangement to form must take place. As illustrated below, these transformations begin with initial deprotonation adjacent to the carbonyl group. The resulting anion then inverts through reversible delocalization of the negative charge into the carbonyl. Next, the chair form of the ring inverts, allowing placement of the bromide and anion into axial positions. At this point, elimination to the cyclohexene occurs.

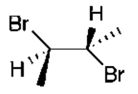


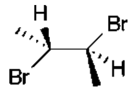
CHAPTER 7 SOLUTIONS

1. *Predict the products of the following reactions and then answer the following questions. Consider stereochemistry.*

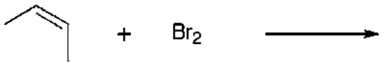
I.

The addition of bromine across a double bond proceeds with attachment of each bromine atom to opposite faces of the starting olefin. In the case of the present example, the products are illustrated below. Please note that the two illustrated products are enantiomers of one another.

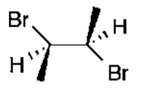


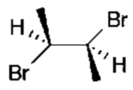


II.

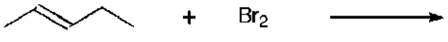


The addition of bromine across a double bond proceeds with attachment of each bromine atom to opposite faces of the starting olefin. In the case of the present example, the products are illustrated below. Please note that the two illustrated products are enantiomers of one another.

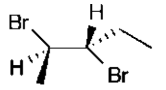


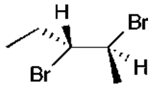


III.

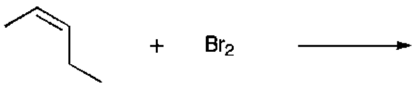


The addition of bromine across a double bond proceeds with attachment of each bromine atom to opposite faces of the starting olefin. In the case of the present example, the products are illustrated below. Please note that the two illustrated products are enantiomers of one another.

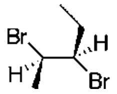


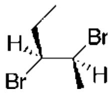


IV.



The addition of bromine across a double bond proceeds with attachment of each bromine atom to opposite faces of the starting olefin. In the case of the present example, the products are illustrated below. Please note that the two illustrated products are enantiomers of one another.





a. *Are the products of reactions I and II the same or are they different? Explain your answer.*

The products of the first two reactions I and II are different. While the mechanistic delivery of a bromine to opposite faces of an olefin is the same for both reactions, the products of reaction I are diastereomers relative to the products of reaction II. The difference in stereochemistry is the result of the olefin of reaction I being *trans* while the olefin of reaction II is *cis*.

b. *How do you account for the products of reactions I and II?*

When the initial addition of bromine to the double bond occurs, the addition takes place on only one side of the molecule. Therefore, the resulting three-membered intermediate retains the geometry of the starting olefin. Nucleophilic attack then occurs from the opposite side of the molecule, thus inverting the stereochemistry at one of the two centers. Since the substrates are symmetrical, only enantiomers are formed in reactions I and II.

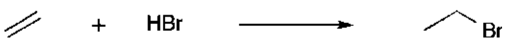
c. *Are the products of reactions III and IV the same or are they different? Explain your answer.*

The products of the first two reactions III and IV are different. While the mechanistic delivery of a bromine to opposite faces of an olefin is the same for both reactions, the products of reaction III are diastereomers relative to the products of reaction IV. The difference in stereochemistry is the result of the olefin of reaction III being *trans* while the olefin of reaction IV is *cis*.

2. *Predict all of the products of the following reactions:*

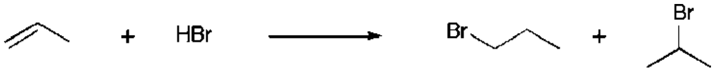
a.

Since the starting olefin is symmetrical, there can be only one product as illustrated below.

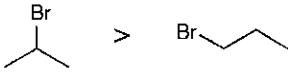


b.

Since the starting olefin is asymmetrical, there are two possible products as illustrated below.

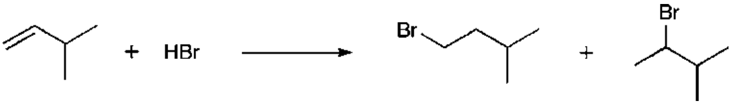


Considering Markovnikov's rule, 2-bromopropane is expected to form in greater quantity compared to 1-bromopropane.

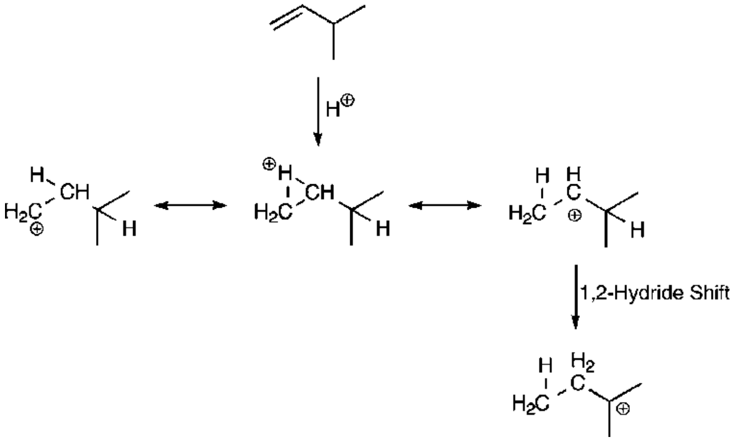


c.

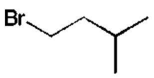
Since the starting olefin is asymmetrical, there are initially only two products to consider as illustrated below.

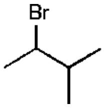


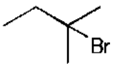
However, recognizing that the initial protonation of the olefin generates positive charges on two adjacent carbon atoms (Scheme 7.6) and that the positive charge at the secondary center is capable of receiving a 1,2-hydride shift (Chapter 5), generation of a tertiary carbocation is possible as illustrated below.



Thus, there are three potential products from this reaction.

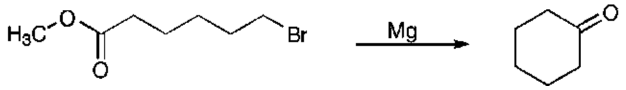




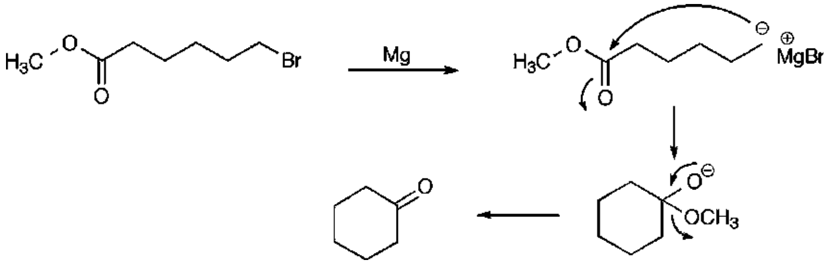


3. *Explain the results of the following reactions. Use arrow pushing and specify mechanistic types.*

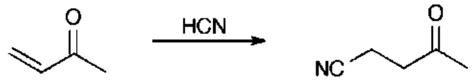
a.



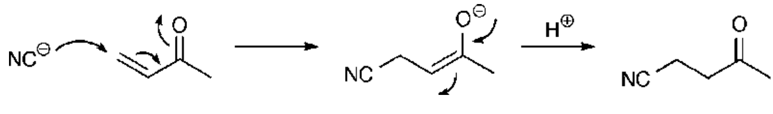
Magnesium reacts with alkyl halides to form alkyl magnesium bromide salts known as Grignard reagents. As mentioned throughout this book, these species bear nucleophilic carbon atoms. As illustrated using arrow pushing, the alkyl anion adds to the carbonyl and subsequently eliminates methoxide. This addition–elimination process leads to the formation of cyclohexanone.



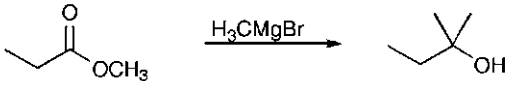
b.



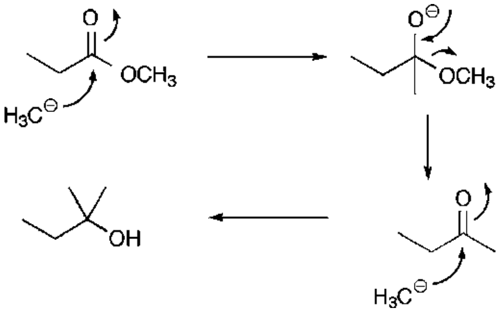
As illustrated using arrow pushing, the cyanide anion adds to the unsaturated ketone via a 1,4-addition.



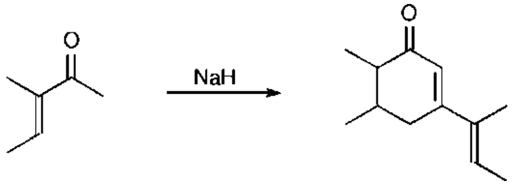
c.



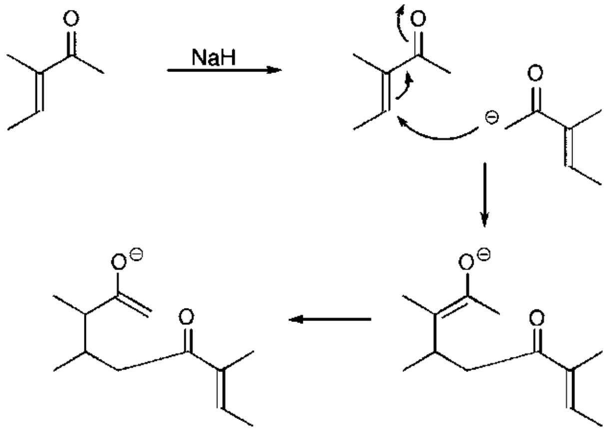
As illustrated using arrow pushing, the first methyl anion drives an addition–elimination reaction forming a ketone. The second methyl anion then adds to the carbonyl in a 1,2-addition, generating the final alcohol.



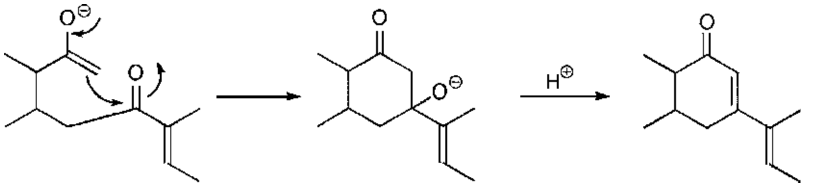
d.



The illustrated product results from a dimerization of the starting material through a multistep process. As illustrated below, initial deprotonation of the starting material with sodium hydride generates an acyl anion that adds, through a 1,4-addition, to the carbonyl of a second starting material molecule. Subsequent proton transfer sets up the intermediate species for an aldol condensation.



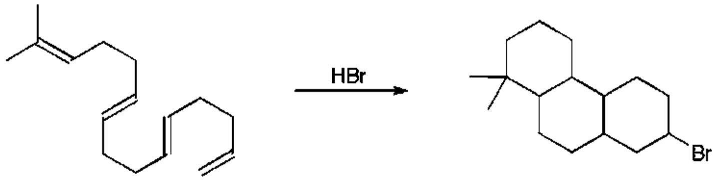
In the second phase of this transformation, illustrated below, a six-membered ring is formed through an intramolecular 1,2-addition. Subsequent protonation of the alkoxide anion and elimination of water generates the final product.



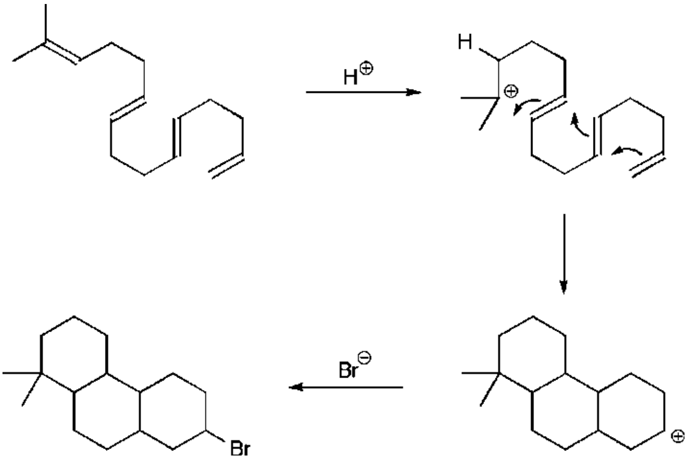
This sequence of steps is known as the Robinson annulation.

4. *Explain the following reactions in mechanistic terms. Show arrow pushing.*

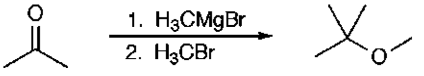
a.



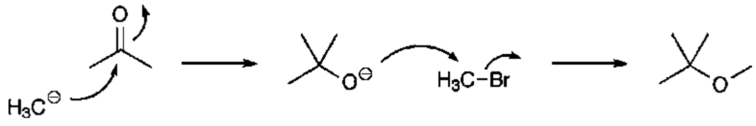
As presented in this chapter, olefins can become protonated under acidic conditions, leading to the formation of electrophilic and cationic carbon atoms. Furthermore, because olefins have nucleophilic character, they can add to sites of positive charge. The cascading of this mechanism, illustrated below, generates polycyclic systems through the cation–π cyclization.



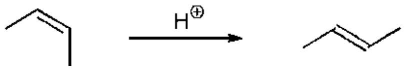
b.



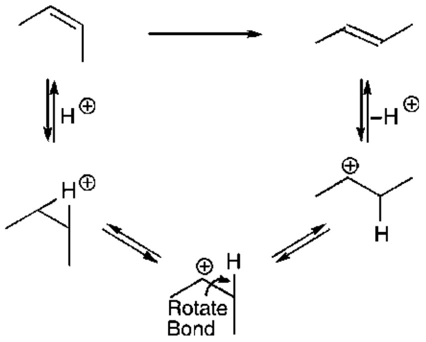
The first step in this sequence is a 1,2-addition of methyl magnesium bromide to acetone. The second step is an S_N2 displacement of bromide with the alkoxide formed in the first step. This two-step process is illustrated below using arrow pushing.



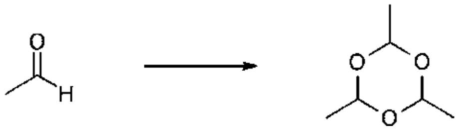
c.



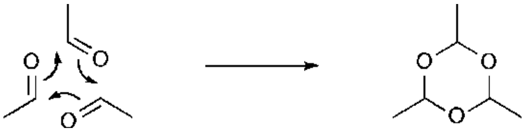
The product of this reaction is the result of a sequence of equilibrium processes. As illustrated below, initial protonation of the *cis*-olefin allows transient formation of single-bond character. This single-bond character then allows for rotation around the central carbon–carbon bond. Final deprotonation liberates the *trans*-olefin. The overall process is driven by the reduced steric interactions present in the *trans*-olefin compared to the *cis*. Specifically, the *cis*-olefin possesses methyl–methyl interactions that are not present in the *trans*.



d.

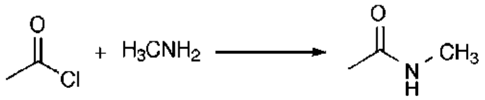


This reaction is a trimerization of acetaldehyde. The mechanism is based on the nucleophilicity of the carbonyl oxygen coupled with the electrophilicity of the carbonyl carbon. The mechanism is illustrated below using arrow pushing.

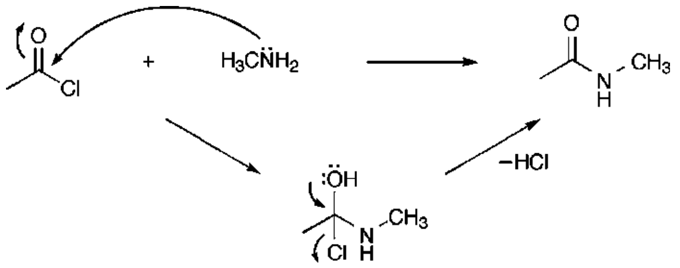


5. *Explain the following products resulting from the reaction of amines with carbonyls. Use arrow pushing and specify mechanistic types.*

a.



This is an addition–elimination reaction involving addition of methylamine to the acid chloride and elimination of hydrochloric acid. The mechanism is illustrated below using arrow pushing.



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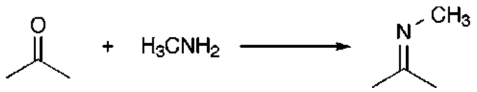
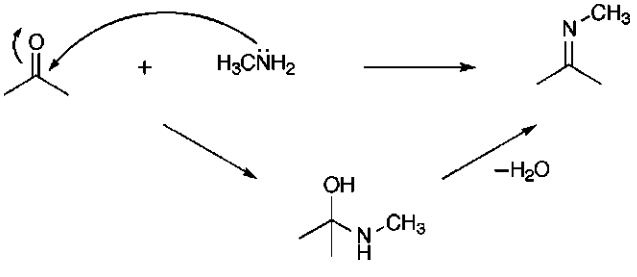
b.



The product of this reaction is an imine resulting from 1,2-addition of methylamine to the carbonyl followed by dehydration. Please note that in the dehydration step, the amine contributes a hydrogen to match the leaving hydroxide group. The mechanism is illustrated below using arrow pushing.



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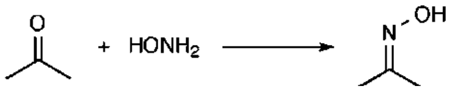
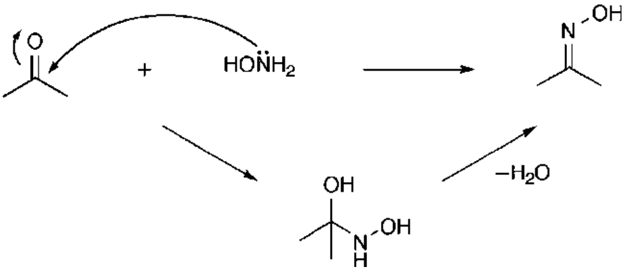
c.



The product of this reaction is an oxime resulting from 1,2-addition of hydroxylamine to the carbonyl followed by dehydration. Please note that in the dehydration step, the amine contributes a hydrogen to match the leaving hydroxide group. The mechanism is illustrated below using arrow pushing.



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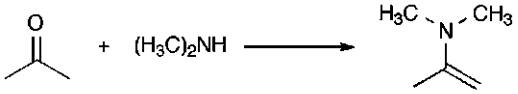
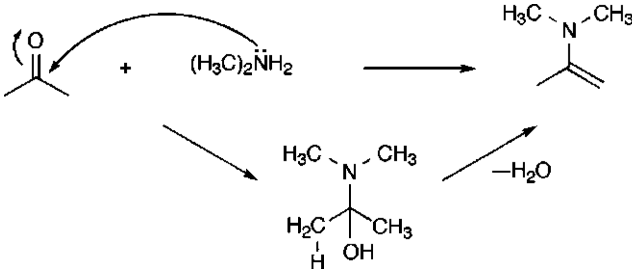
d.



The product of this reaction is an enamine resulting from 1,2-addition of dimethylamine to the carbonyl followed by dehydration. Please note that in the dehydration step, an adjacent methyl group contributes a hydrogen to match the leaving hydroxide group. The mechanism is illustrated below using arrow pushing.



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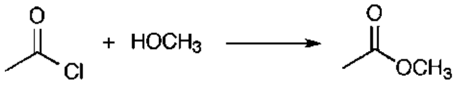
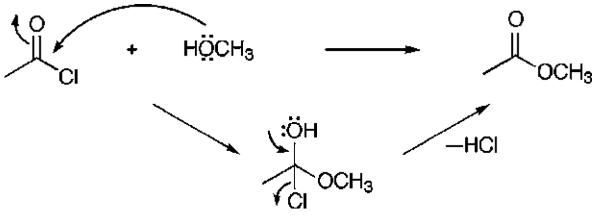
6. *Provide mechanisms for the following reactions. Show arrow pushing.*

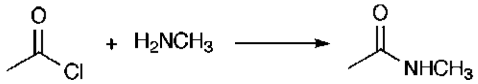
a.



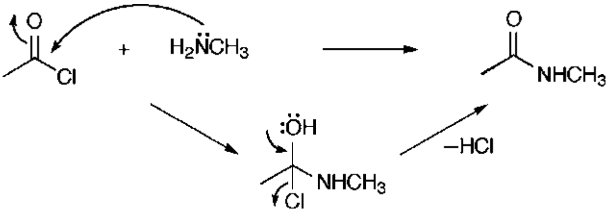
This is an addition–elimination reaction of methanol with acetyl chloride forming methyl acetate. As illustrated below using arrow pushing, methanol is being added while hydrochloric acid is being eliminated. The driving force behind this reaction lies with the relative electronegativities of chlorine and oxygen. Chlorine being more electronegative than oxygen translates to a chlorine anion (chloride) being a better leaving group than an oxygen anion (alkoxide).



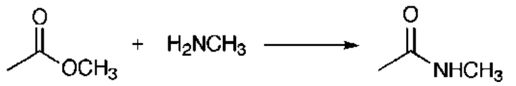
b.



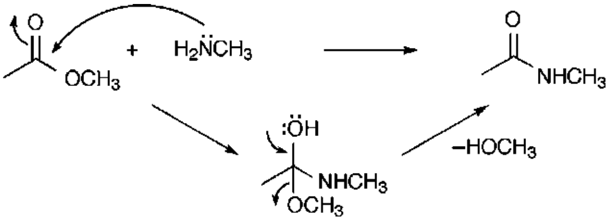
This is an addition–elimination reaction of methylamine with acetyl chloride forming methyl acetamide. As illustrated below using arrow pushing, methylamine is being added while hydrochloric acid is being eliminated. The driving force behind this reaction lies with the relative electronegativities of chlorine and nitrogen. Chlorine being more electronegative than nitrogen translates to a chlorine anion (chloride) being a better leaving group than a nitrogen anion (amide).



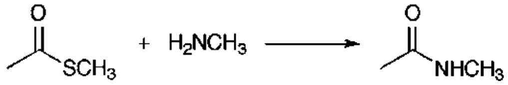
c.



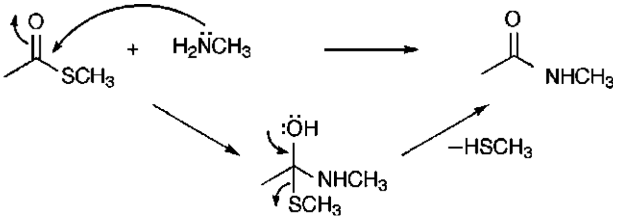
This is an addition–elimination reaction of methylamine with methyl acetate forming methyl acetamide. As illustrated below using arrow pushing, methylamine is being added while methanol is being eliminated. The driving force behind this reaction lies with the relative electronegativities of oxygen and nitrogen. Oxygen being more electronegative than nitrogen translates to an oxygen anion (alkoxide) being a better leaving group than a nitrogen anion (amide).



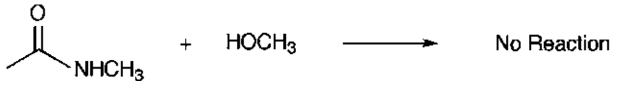
d.



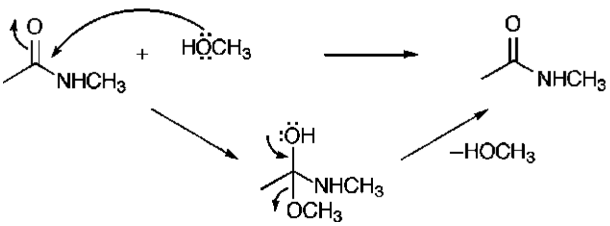
This is an addition–elimination reaction of methylamine with methyl thioacetate forming methyl acetamide. As illustrated below using arrow pushing, methylamine is being added while methanethiol is being eliminated. The driving force behind this reaction lies with the relative polarizabilities of sulfur and nitrogen. Sulfur being more polarizable than nitrogen translates to a sulfur anion (sulfide) being a better leaving group than an nitrogen anion (amide).



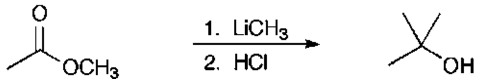
e.



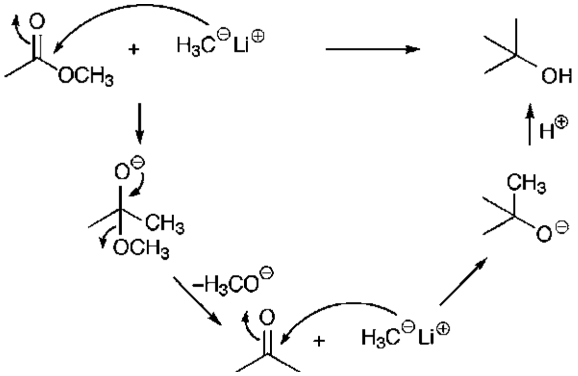
The failure of this attempted addition–elimination reaction is driven by the relative electronegativities of oxygen and nitrogen. Oxygen being more electronegative than nitrogen translates to an oxygen anion (alkoxide) being a better leaving group than a nitrogen anion (amide). Thus, while methanol may add to the amide, methanol will be the only group eliminated and there will be no net reaction.



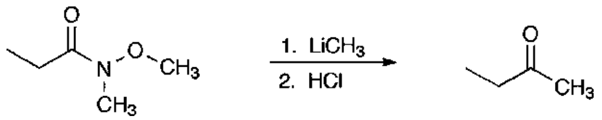
f.



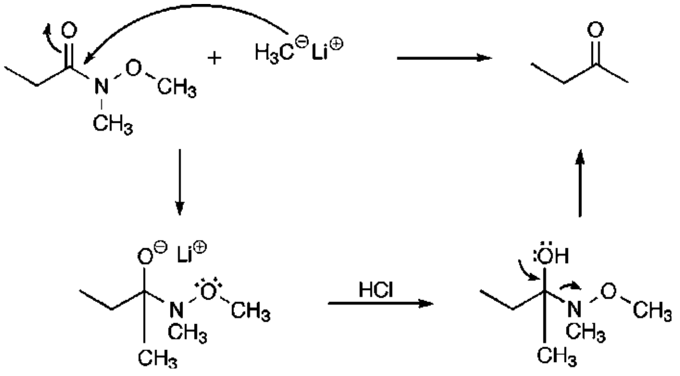
This is a two-step transformation. The first step is an addition–elimination reaction of methyllithium with methyl acetate transiently forming acetone. The second step is a 1,2-addition of methyllithium to acetone forming the final *tert*-butyl alcohol. Hydrochloric acid is present only to quench the formed anions and liberate a neutral product. The steps of this transformation are illustrated below using arrow pushing. Please note that, for simplicity, association of the lithium cations with the anions of the illustrated mechanistic pathway is not shown.



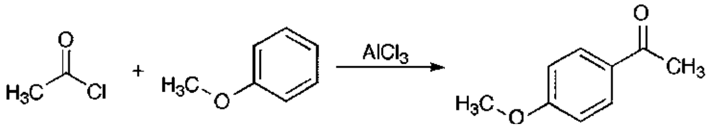
g.



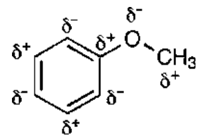
This is an addition–elimination reaction of methyllithium with *N*-methyl-*N*-methoxypropionamide forming 2-butanone. As illustrated below using arrow pushing, methyllithium initially adds to the amide. Unlike the process illustrated in Problem 6(f), a second methyllithium does not add and an alcohol is not formed. This is explained by the ability of lithium to coordinate between the two present oxygen atoms. The first is the oxygen of the former carbonyl and the second is the oxygen associated with the methoxy component of the illustrated amide. Due to the stability of this type of five-membered interaction, initial collapse of the anionic intermediate with loss of *N*-methyl-*N*-methoxyamine is prevented. In Problem 6(f), collapse of the anionic intermediate led to regeneration of a carbonyl capable of reacting with a second methyllithium. In this example, this does not happen, and quenching with hydrochloric acid allows exclusive formation of the ketone shown. This process is illustrated below using arrow pushing.



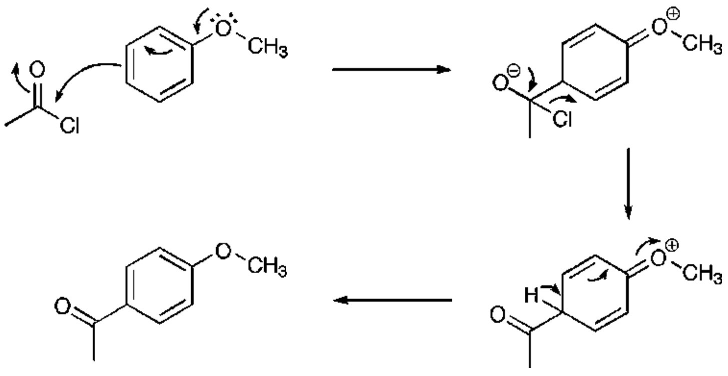
h.



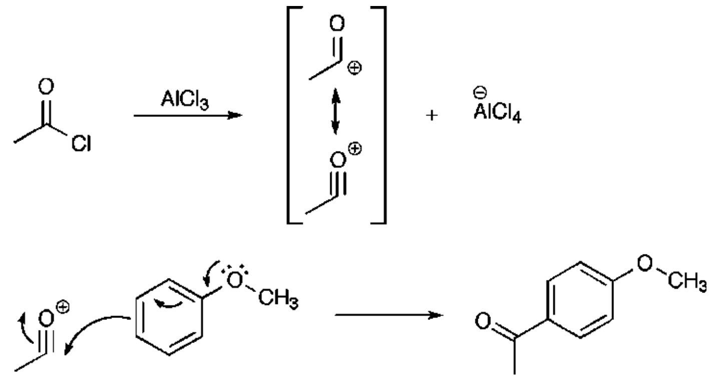
Just as double bonds possess nucleophilic characteristics, so do aromatic rings. By analyzing the charge distribution around an aromatic ring, sites of partial positive charge and sites of partial negative charge can be identified. The sites of partial positive charge are electrophilic in nature, and the sites of partial negative charge are nucleophilic in nature. The partial charge distribution for methoxybenzene was the subject of Problem 2(h) from Chapter 1 and is shown below.



Having identified the nucleophilic sites, this mechanism now becomes an addition–elimination reaction between methoxybenzene and acetyl chloride where methoxybenzene is being added and chloride is being eliminated. As shown below, using arrow pushing, electron movement starts with the methoxy oxygen and moves through the aromatic ring. The addition–elimination steps occur as shown in Problem 6(a). Finally, due to the conjugated and charged system, the proton present on the reactive carbon atom of the phenyl ring becomes acidic. Loss of this proton allows rearomatization and neutralization of the cationic intermediate, thus allowing conversion to the final product.

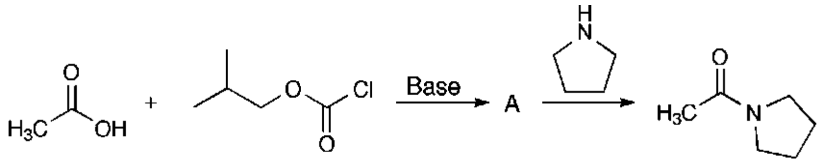


The reaction presented in this problem is known as a Friedel–Crafts acylation. Technically, this example belongs to a class of reactions referred to as electrophilic aromatic substitutions. Furthermore, the actual mechanism associated with this reaction, utilizing Lewis acid reagents as catalysts, proceeds through initial formation of an electrophilic acyl cation followed by reaction with an aromatic ring acting as a nucleophile. This mechanism, shown below, reflects distinct parallels to standard addition–elimination reaction mechanisms warranting introduction at this time.

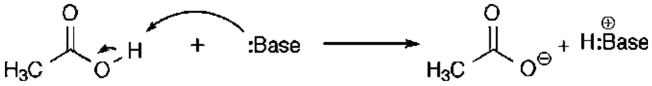


7. *Explain the following amide-forming reactions using arrow pushing. Specify the structures of **A**, **B**, and **C** and show all relevant mechanistic steps.*

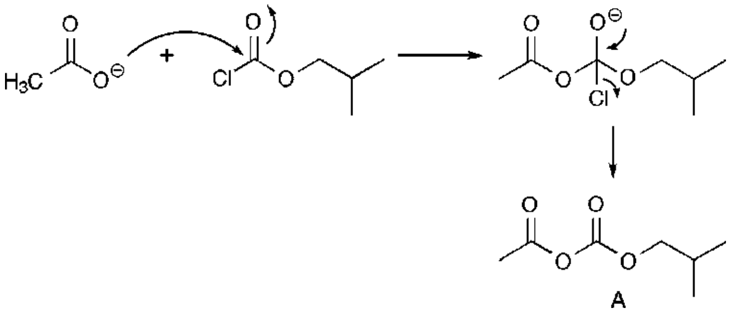
a.



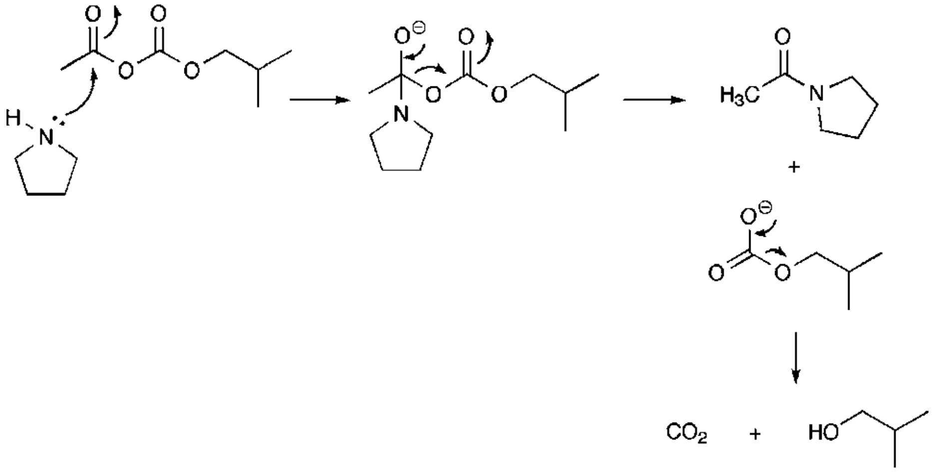
The first step of this sequence is deprotonation of the carboxylic acid by an amine base.



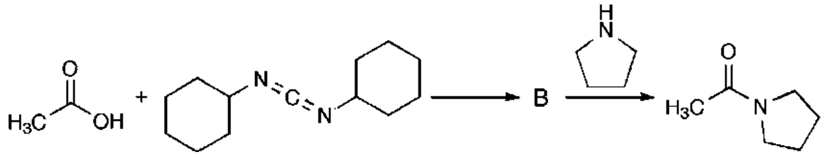
Next, the carboxylate anion participates in an addition–elimination reaction with isobutyl chloroformate. Elimination of a chloride anion results in formation of intermediate **A**. These reactions are generally facilitated by the introduction of an amine base such as triethylamine (not shown in this problem). The mechanism is illustrated below using arrow pushing, and the illustrated product belongs to a class of compounds known as mixed carbonic anhydrides.



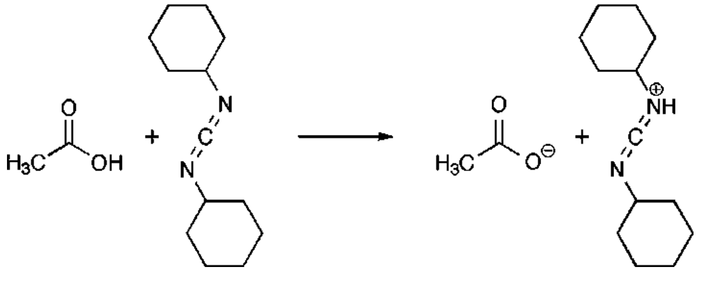
Mixed carbonic anhydrides are a form of activated esters that can react with amines to form amides. The addition–elimination mechanism, illustrated below using arrow pushing, involves addition of an amine followed by an elimination step driven by the release of carbon dioxide.



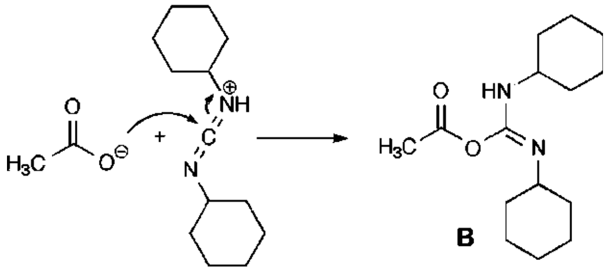
b.



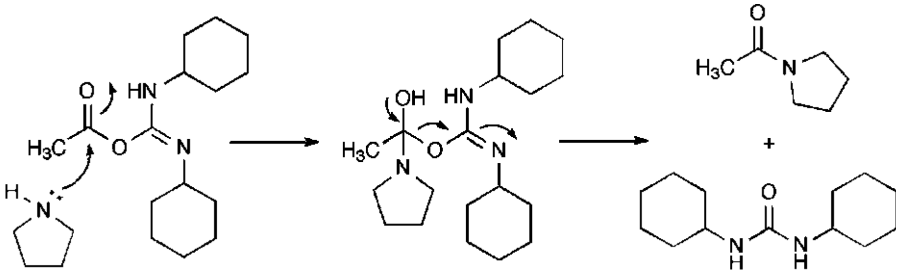
As with Problem 7(a), the first step in this reaction is a proton transfer. In this case, the base is a nitrogen atom present on dicyclohexylcarbodiimide.



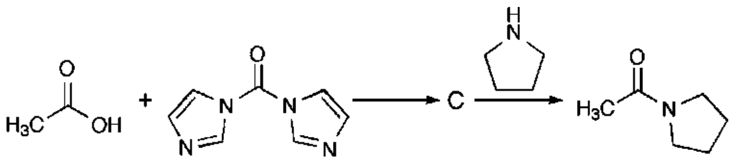
Following proton transfer, the resulting carboxylate anion adds to the protonated dicyclohexylcarbodiimide.



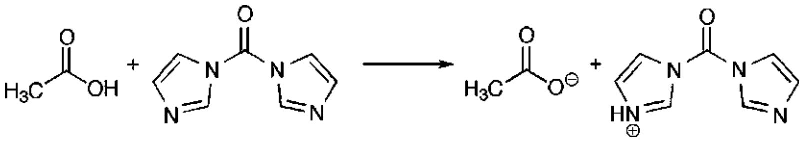
Like the mixed carbonic anhydride (intermediate **A** from Problem 7(a)), intermediate **B** is an active ester that can react with amines to form amides. The addition–elimination mechanism, illustrated below using arrow pushing, involves addition of an amine followed by elimination of dicyclohexylurea.



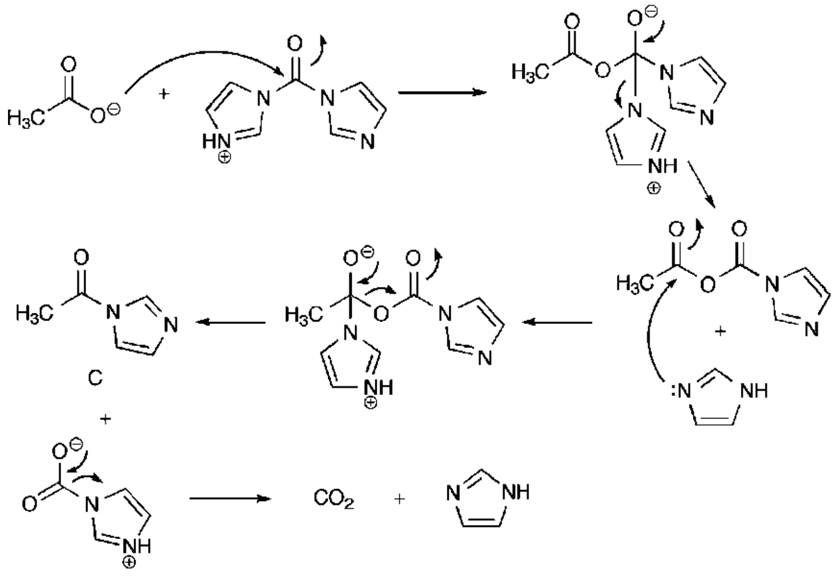
c.



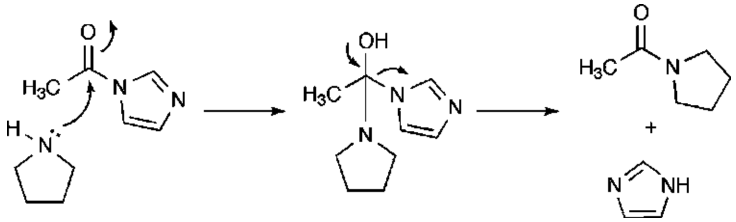
Like Problems 7(a) and 7(b), the first step of this reaction is a proton transfer. In this case, the basic nitrogen is a nitrogen atom present on carbonyl diimidazole.



Following proton transfer, the carboxylate anion participates in an addition–elimination reaction where the carboxylate anion adds to the carbonyl of carbonyl diimidazole and imidazole is eliminated. Intermediate **C** then results from a second addition–elimination step where imidazole adds to the resulting anhydride species, and the group being eliminated decomposes to carbon dioxide and imidazole. This sequence of events is illustrated below using arrow pushing.



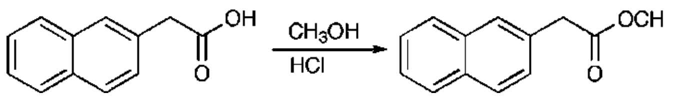
Like the mixed carbonic anhydride (intermediate **A** from Problem 7(a)), the intermediate imidazolide (intermediate **C**) is an activated carboxy group that can react with amines to form amides. The addition–elimination mechanism, illustrated below using arrow pushing, involves addition of an amine followed by elimination of imidazole.



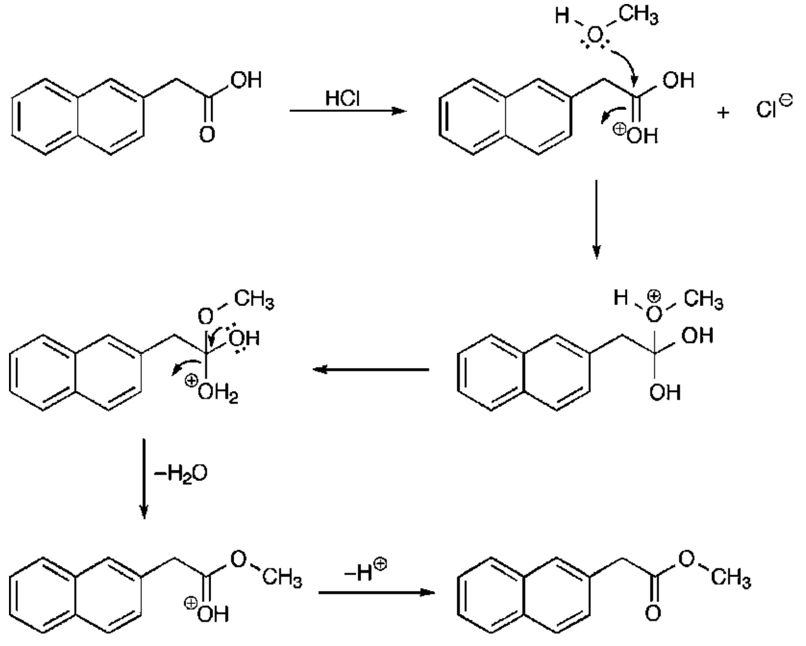
CHAPTER 8 SOLUTIONS

1. *Describe the following functional group transformation in mechanistic terms. Show arrow pushing.*

a.

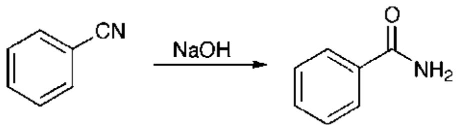


This is an addition–elimination reaction between methanol and a protonated carboxylic acid. As illustrated below, hydrochloric acid protonates the carboxylic acid. Methanol then adds to the protonated carboxylic acid. Elimination of water liberates the methyl ester.

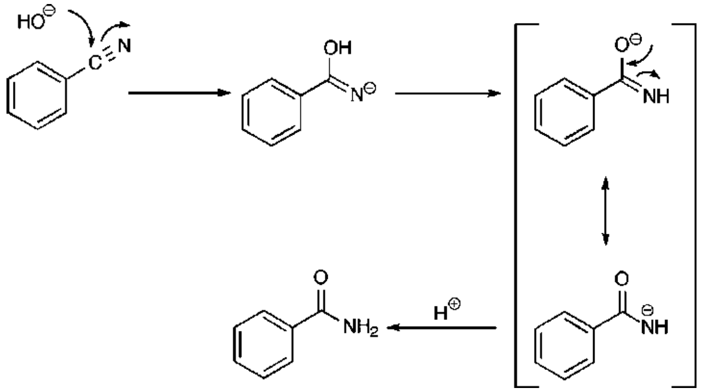


Please note that this reaction is generally run with methanol as the solvent. Under these circumstances, the reverse reaction, ester hydrolysis, does not proceed because the water being liberated during the reaction is so dilute in the methanol that water molecules never interact with the forming ester.

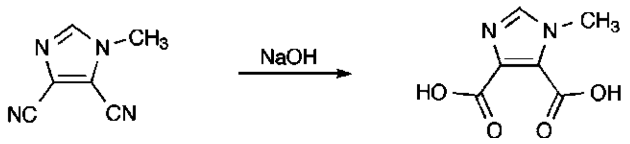
b.



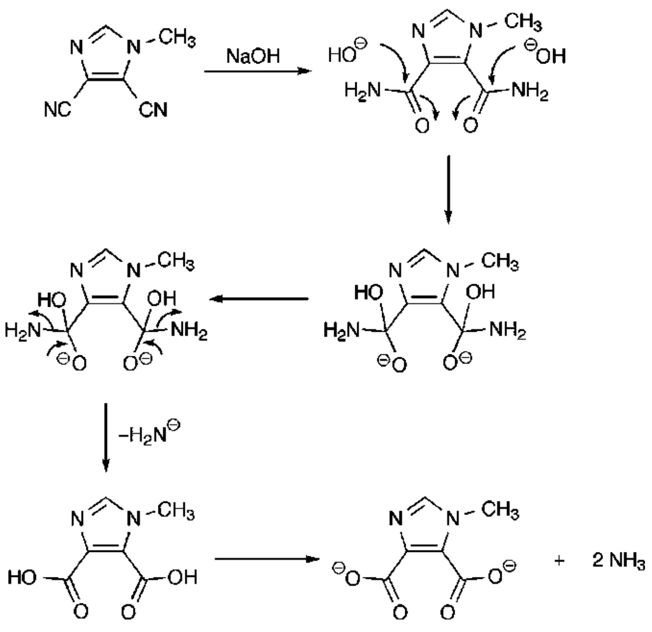
This is a hydrolysis reaction where a hydroxide anion adds to a nitrile. As illustrated below, the hydroxide anion adds to the nitrile carbon atom. Proton transfer from the hydroxyl group to the nitrogen anion is followed by charge transfer through resonance. This charge transfer results in formation of a carbonyl and a nitrogen anion. The nitrogen anion is neutralized when the reaction is quenched with acid.



c.



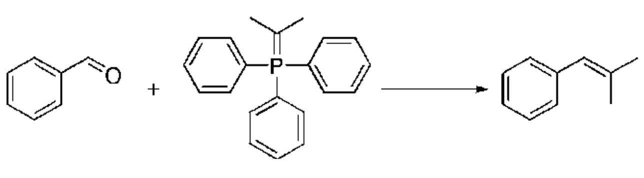
The first step in this reaction is the hydrolysis of two nitrile groups to form amides. The mechanism for the amide formation is identical to that illustrated in the previous example. Continuing from the amides, hydroxide anions add to the carbonyls, generating negative charges on each functional group. Following the addition–elimination mechanistic sequence, the negative charges residing on the oxygen atoms displace amine anions (amide ions), liberating the illustrated carboxylic acids. However, since ammonia is less acidic than a carboxylic acid, the amine anions deprotonate the carboxylic acids, generating carboxylate anions and ammonia. These carboxylate anions become neutralized on treatment with acid. In order to simplify the presentation of this mechanism, associated sodium cations are omitted. It is understood that each negative charge is associated with a sodium cation.



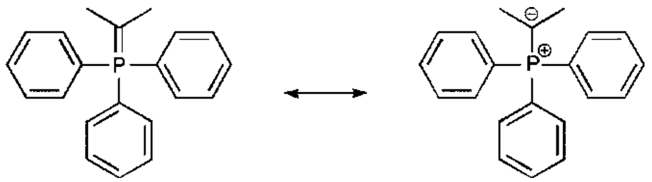
Please note that this reaction generally requires strongly basic conditions and high temperatures and that the hydrolyses probably occur one at a time.

2. *Explain the following reactions in mechanistic terms. Show arrow pushing and describe the reaction as a name reaction.*

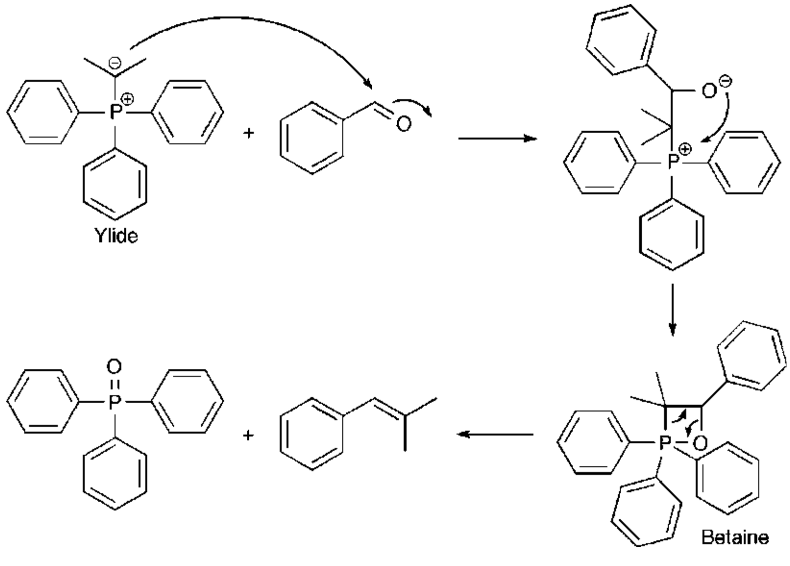
a.



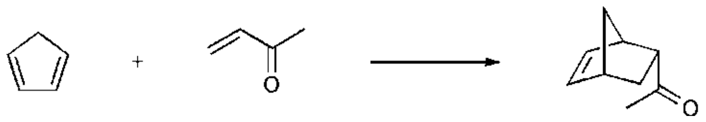
This is an example of the Wittig reaction which occurs when a phosphorus ylide reacts with an aldehyde or a ketone. An ylide is a molecule in which there exists a natural state of charge separation. In this case, the ylide is isopropylidene triphenylphosphorane, illustrated below. Note that the phosphorus possesses a positive charge and is electrophilic while the negative charge resides on a carbon atom, rendering it nucleophilic.



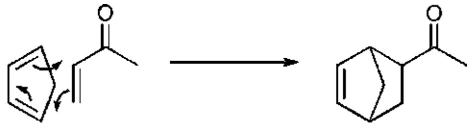
The Wittig reaction mechanism involves addition of the anionic carbon atom to the carbon atom of an aldehyde. As illustrated below, the now negatively charged oxygen atom adds to the positively charged phosphorus atom, forming a four-membered ring. This ring, known as a betaine, then decomposes to form an olefin and triphenylphosphine oxide.



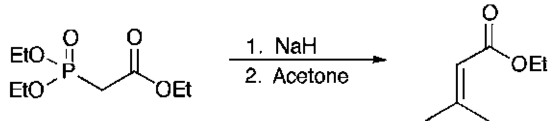
b.



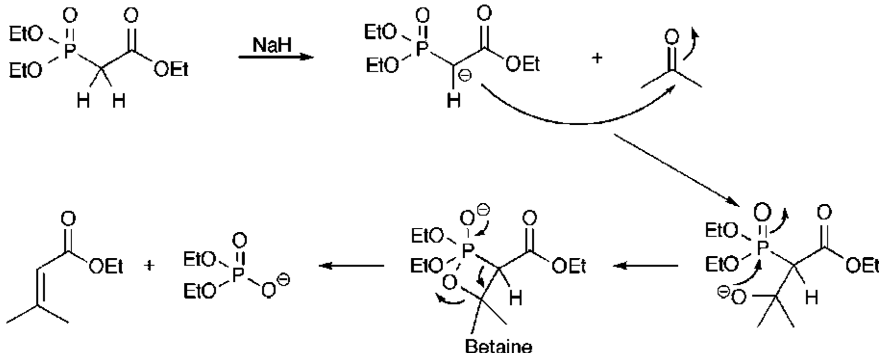
This is an example of a Diels–Alder reaction. This is an electrocyclic reaction where no charges are involved. While no charges are involved, electron pairs do move and their movement can be illustrated using arrow pushing. The mechanism, illustrated below, involves aligning cyclopentadiene (a diene) with methyl vinyl ketone (a dienophile) such that all three double bonds define a six-membered ring. Once the six-membered ring is defined, the electrons simply move to form two new carbon–carbon bonds with a net conversion of two carbon–carbon double bonds to carbon–carbon single bonds. It is important to recognize that in electrocyclic reactions, the total number of bonds never changes. Specifically, seven bonds are involved in the reaction where six of the seven bonds are incorporated in double bonds. Upon conclusion of the reaction, these seven bonds comprise five carbon–carbon single bonds and one carbon–carbon double bond.



c.

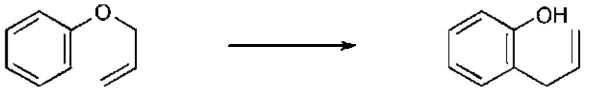


This is an example of a Horner–Emmons reaction. The mechanism, illustrated below, is similar to that discussed for Problems 7(n) and 7(o) from Chapter 4. As shown, the first step involves deprotonation of triethyl phosphonoacetate with sodium hydride. The resulting anion then participates in an addition reaction with acetone. The product of this addition reaction possesses a negatively charged oxygen. This negatively charged oxygen adds into the phosphorus–oxygen double bond, forming a four-membered ring known as a betaine. The betaine, on decomposition as illustrated with arrow pushing, liberates the product.

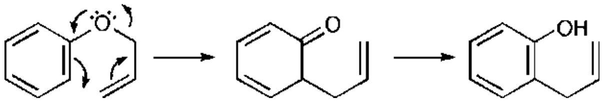


When considering the Horner–Emmons reaction, it is important to recognize that the mechanism and products are similar to those observed during a Wittig reaction. In fact, the Horner–Emmons reaction is a recognized and viable alternative to the Wittig reaction.

d.

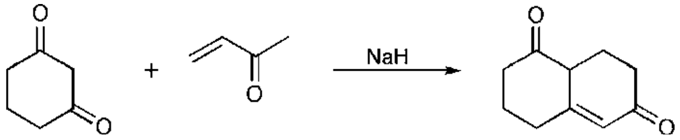


This is an example of a Claisen rearrangement which is an electrocyclic reaction where no charges are involved. While no charges are involved, like the Diels–Alder reaction, electron pairs do move and their movement can be illustrated using arrow pushing. The mechanism, illustrated below, involves moving a lone pair of electrons from the oxygen into the aromatic ring. The aromatic ring then adds electrons to the double bond. The double bond then migrates and the carbon–oxygen bond is cleaved. While the expected product may be the illustrated ketone, spontaneous conversion to the enol form is facilitated by the stability of the resulting aromatic ring. Thus the illustrated product is formed.

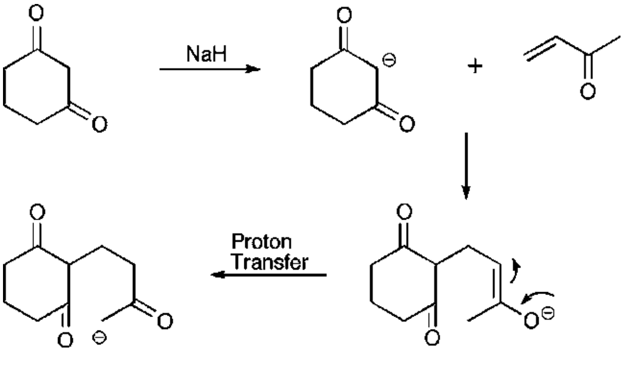


When considering the above mechanistic description, it is important to recognize that all of these steps occur concurrently. Furthermore, like the Diels–Alder reaction (and all electrocyclic reactions), there is no net loss or gain of bonds.

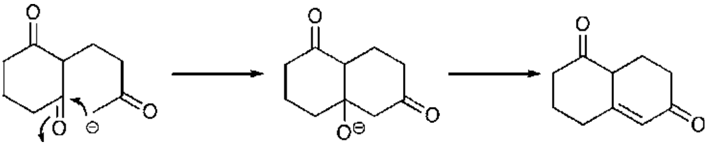
e.



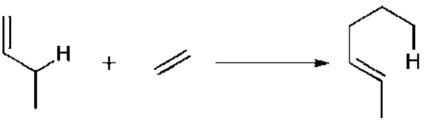
This is an example of a Robinson annulation. The mechanism for the Robinson annulation involves a sequence of conjugate addition reactions and aldol condensations. As illustrated, the first step is deprotonation of cyclohexanedione with sodium hydride. The resulting anion then participates in a 1,4-addition to methyl vinyl ketone. The resulting enolate anion then tautomerizes through resonance, placing the anion adjacent to a carbonyl. Proton transfer migrates this negative charge to the terminal methyl group.



Following formation of a negative charge at the terminal methyl group, the terminal methyl group participates in an aldol condensation with one of the cyclohexanedione carbonyl groups. This aldol condensation involves initial addition of the anion to the carbonyl followed by subsequent dehydration of the resulting alkoxide. This dehydration usually occurs under acidic conditions during isolation of the product and through mechanistic pathways already presented (consider protonation of a hydroxyl group followed by an E1 elimination under solvolytic conditions).

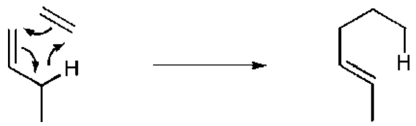


3. *Explain the following name reactions in mechanistic terms. Show arrow pushing.*
   - **a.** *The ene reaction*

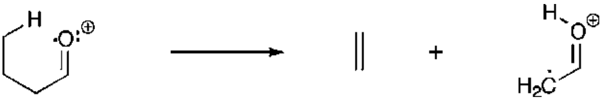


Note: Only the hydrogen involved in the reaction is shown.

The ene reaction is an electrocyclic reaction similar to the Diels–Alder reaction and the Claisen rearrangement. In this reaction, a hydrogen atom is participating in the electrocyclic process. The mechanism, illustrated below using arrow pushing, involves no charges. Note that there is no net gain or loss of bond count between the starting materials and the product.

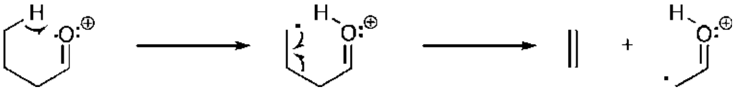


b. *The McLafferty rearrangement*

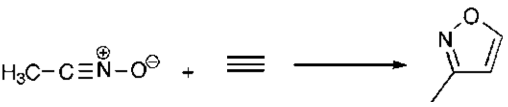


Note: The radical cation present in the starting material is the result of the carbonyl oxygen losing a single electron. This reaction is generally observed during electron impact mass spectrometry.

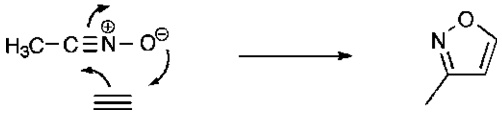
The McLafferty rearrangement is a reaction generally seen as part of the fragmentation processes observed during mass spectrometry. It is, in fact, during electron impact mass spectrometry that the illustrated starting radical cation is formed. Since this is a radical mediated process, there are no charges involved in the progression of the reaction mechanism other than the positive charge that remains on the oxygen atom. As shown below, using arrow pushing, the first step of this rearrangement involves transfer of a hydrogen atom to the carbonyl oxygen. This occurs through homolytic bond cleavage and bond formation. The second step, also progressing through a homolytic process, involves cleavage of a carbon–carbon bond and liberation of ethylene.



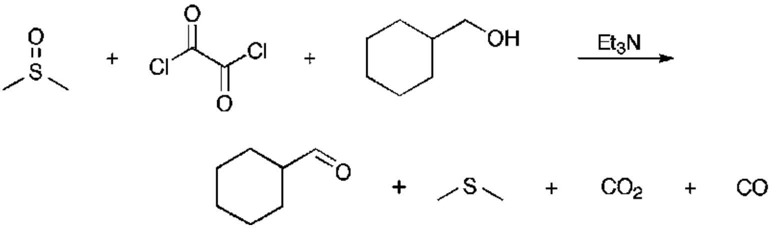
c. *1,3-Dipolar cycloaddition*



1,3-Dipolar cycloadditions are electrocyclic reactions where one of the starting materials is charged. In fact, the charges on the starting material define the dipole. Like all electrocyclic reactions, there is no net gain or loss of bond count. However, in this case, while the starting material is charged, there are no charges present on the product. The mechanism of this reaction is illustrated below using arrow pushing.

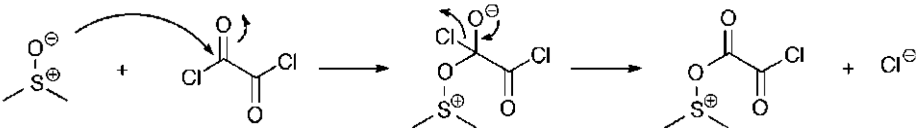


d. *The Swern oxidation*

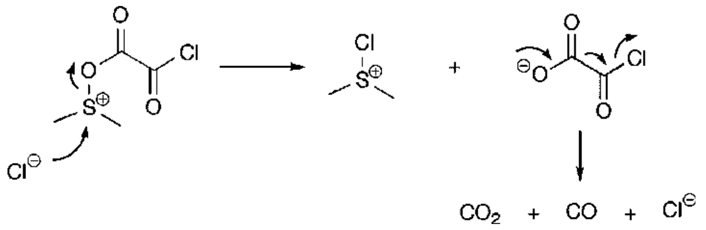


Hint: The oxygen atom in dimethyl sulfoxide is nucleophilic.

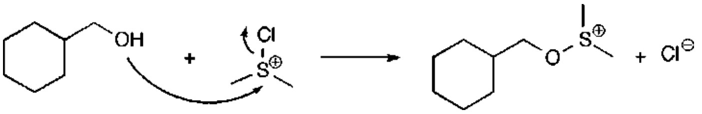
In this book, there have been many references to oxidation and reduction reactions. While these reactions are not within the scope of the discussions of this book, their mechanisms do involve the processes presented herein. In the case of the Swern oxidation, the first step is an addition–elimination reaction between dimethyl sulfoxide and oxallyl chloride. This process, illustrated below using arrow pushing, involves addition of the sulfoxide oxygen to a carbonyl with subsequent elimination of a chloride anion.



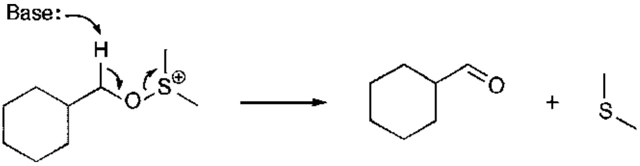
The second stage of the Swern oxidation, illustrated below, involves a nucleophilic displacement of the oxallyl group from the sulfur. In this step, the nucleophile is a chloride anion, and the reaction is facilitated by the decomposition of the leaving group into carbon dioxide gas, carbon monoxide gas, and a chloride anion.



The third stage of this reaction involves another nucleophilic displacement. In this step, the nucleophile is an alcohol and the leaving group is a chloride anion. This step, illustrated below, involves protonation of the leaving chloride anion forming hydrochloric acid.

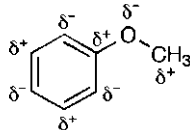


The final stage of this reaction involves an E2 elimination. In this step, illustrated below, a proton adjacent to the oxygen is removed by a base such as triethylamine. The negative charge then forms a double bond with the oxygen and dimethylsulfide is eliminated. The overall oxidation process converts an alcohol into an aldehyde.

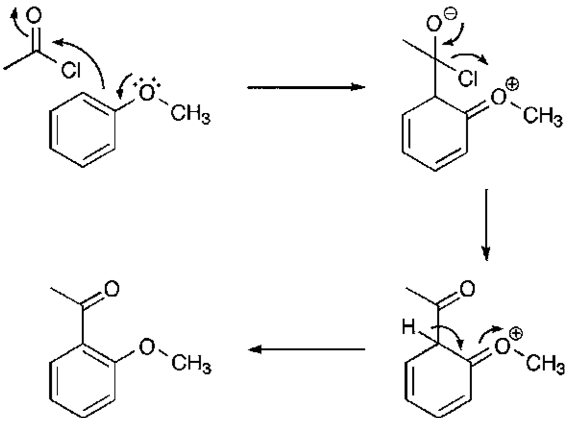


4. *The Friedel–Crafts acylation, illustrated in Scheme 8.12, shows the formation of one product. However, the reaction, as illustrated, actually forms a mixture of two products. Using the arguments presented in the solution set for Chapter 7, identify the second product. Show partial charges and arrow pushing.*

Just as double bonds possess nucleophilic characteristics, so do aromatic rings. By analyzing the charge distribution around an aromatic ring, sites of partial positive charge and sites of partial negative charge can be identified. The sites of partial positive charge are electrophilic in nature and the sites of partial positive charge are nucleophilic in nature. The partial charge distribution for methoxybenzene was the subject of Problem 2(h) from Chapter 1 and is shown below.



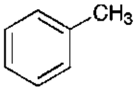
Having identified the nucleophilic sites, this mechanism now becomes an addition–elimination reaction between methoxybenzene and acetyl chloride where methoxybenzene is being added and chloride is being eliminated. As shown below, using arrow pushing, electron movement starts with the methoxy oxygen and moves through the aromatic ring. The addition–elimination steps occur as shown in Problem 6(a). Finally, due to the conjugated and charged system, the proton present on the reactive carbon atom of the phenyl ring becomes acidic. Loss of this proton allows rearomatization and neutralization of the cationic intermediate, thus allowing conversion to the final product.



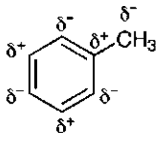
Please note that while the Friedel–Crafts acylation reaction is presented in discussions of addition–elimination reaction mechanisms, this reaction is actually an electrophilic aromatic substitution reaction. The correct mechanisms for a Freidel–Crafts acylation was presented in the solution for Problem 6 (h) from Chapter 7.

5. *Predict all products formed from a Friedel–Crafts acylation on the following compounds with acetyl chloride. Rationalize your answers using partial charges.*

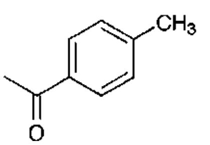
a.

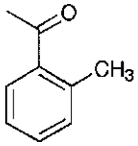


Identification of the partial charges on toluene (methylbenzene), illustrated below, was the subject of Problem 2(g) in Chapter 1.

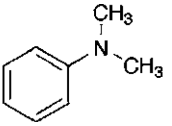


Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the two structures shown below.

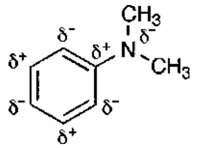




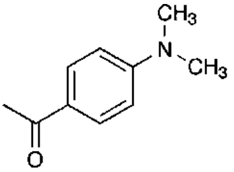
b.

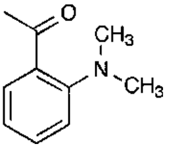


Like methoxybenzene (see Problem 4 in this chapter and Problem 2(h) from Chapter 1), the partial charges of dimethylaniline (dimethylaminobenzene) are dependent upon the electron-donating properties of nitrogen. Thus, the partial charges are distributed as shown below.

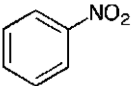


Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the two structures shown below.

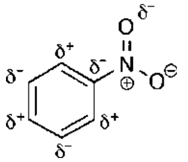




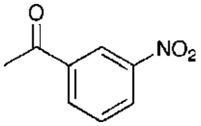
c.



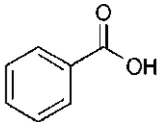
Identification of the partial charges on nitrobenzene, illustrated below, was the subject of Problem 2(j) in Chapter 1.



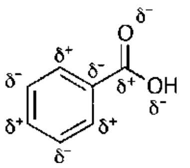
Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the structure shown below. Please note that while there are two carbon atoms bearing partial negative charges, acylation of each of these leads to the formation of identical products.



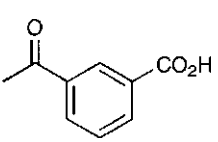
d.



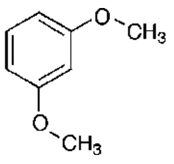
Identification of the partial charges on benzoic acid, illustrated below, was the subject of Problem 2(k) in Chapter 1.



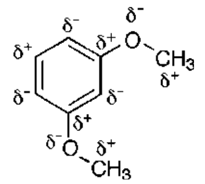
Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the structure shown below. Please note that while there are two carbon atoms bearing partial negative charges, acylation of each of these leads to the formation of identical products.



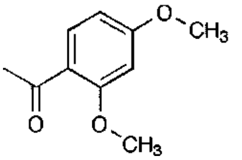
e.

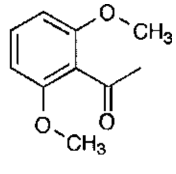


Extrapolating from the arguments presented in Problem 2(h) of Chapter 1, the partial charge distribution of 1,3-dimethoxybenzene is as shown below.

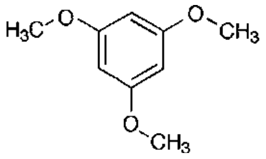


Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the two structures shown below. Please note that while there are three carbon atoms bearing partial negative charges, acylation of two of these leads to the formation of identical products.

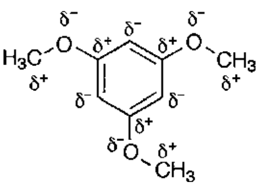




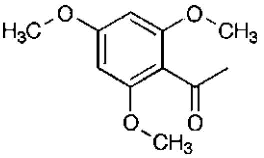
f.



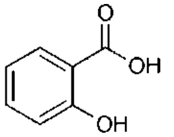
Extrapolating from the arguments presented in Problem 2(h) of Chapter 1, the partial charge distribution of 1,3,5-trimethoxybenzene is as shown below.

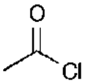


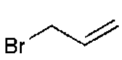
Based on the arguments presented in Chapter 7 and in Problem 4 of this chapter, acylation leads to the formation of the structure shown below. Please note that while there are three carbon atoms bearing partial negative charges, acylation of each of these leads to the formation of the same product.

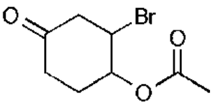


6. *From the following list of compounds propose a synthetic strategy for the specified compounds. Up to four synthetic steps may be required. Any chemical reagents may be used. Show all arrow pushing.*

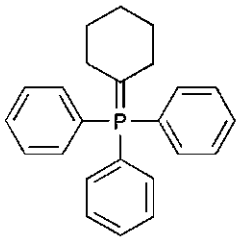


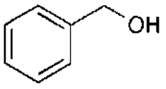


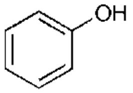


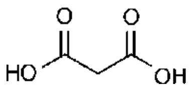


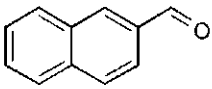
H_3C-OH

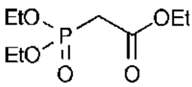






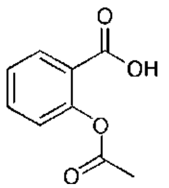






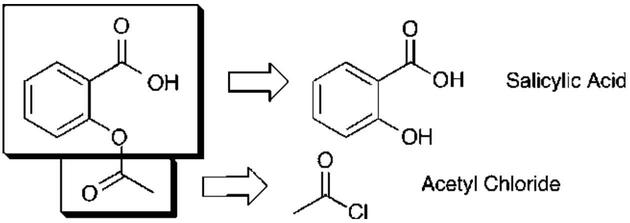
H_3C —I

a.

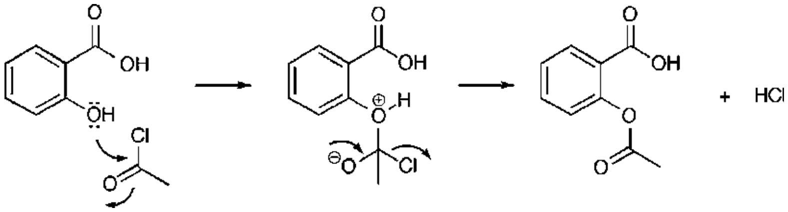


(Acetylsalicylic acid, aspirin)

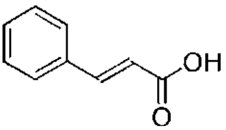
Acetylsalicylic acid, a common pain reliever, is composed of two fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to salicylic acid and acetyl chloride.



The reaction between salicylic acid and acetyl chloride is an addition–elimination reaction where the hydroxyl group of salicylic acid adds to the carbonyl of acetyl chloride. This addition is followed by the elimination of hydrochloric acid as shown below.

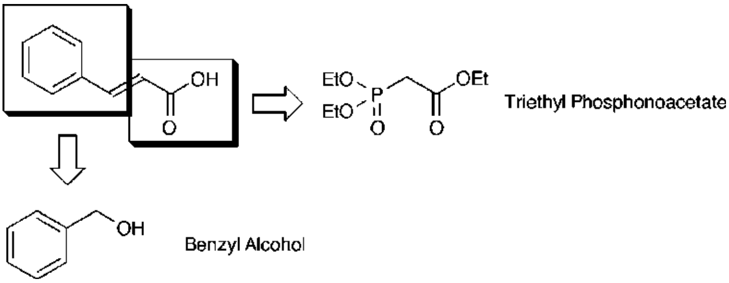


b.



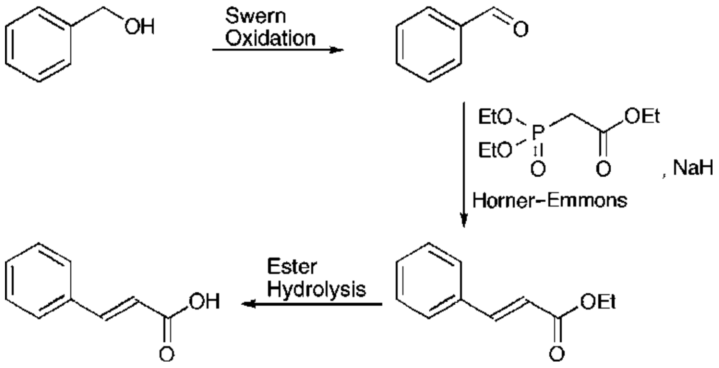
(*Cinnamic acid*)

Cinnamic acid, the active flavor compound in cinnamon, is composed of two fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to benzyl alcohol and triethyl phosphonoacetate.

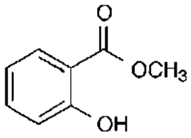


The combination of these compounds will generate cinnamic acid through the synthetic sequence illustrated below. As shown, benzyl alcohol is oxidized to benzaldehyde using the Swern oxidation. Next, the aldehyde is reacted with triethyl phosphonoacetate by applying the Horner–Emmons reaction. Finally, the ester is hydrolyzed to a carboxylic acid. With arrow pushing, the mechanism for the

Swern oxidation is shown in Problem 3(d) of this chapter, the mechanism for the Horner–Emmons reaction is shown in Problem 2(c) of this chapter, and the mechanism for base-mediated ester hydrolysis was highlighted in Scheme 7.19.

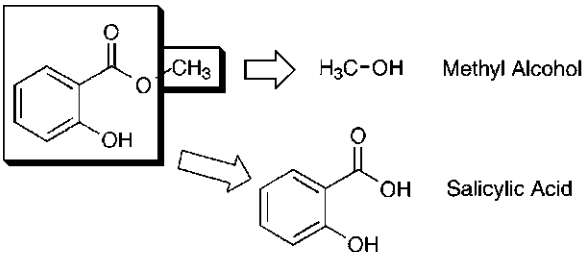


c.

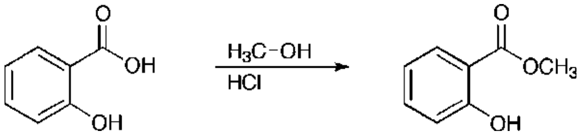


(*Methyl Salicylate, oil of Wintergreen*)

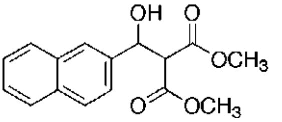
Methyl salicylate, the active flavor compound in wintergreen candy, is composed of two fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to salicylic acid and methyl alcohol.



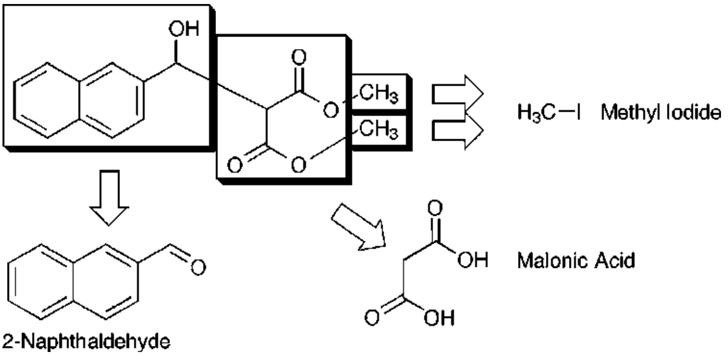
The combination of these compounds will generate methyl salicylate when conditions for an acid-mediated esterification, illustrated below, are applied. The mechanism for this type of ester-forming reaction is shown in Problem 1(a) of this chapter.



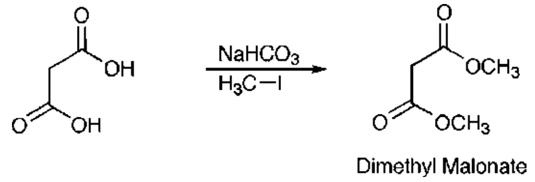
d.



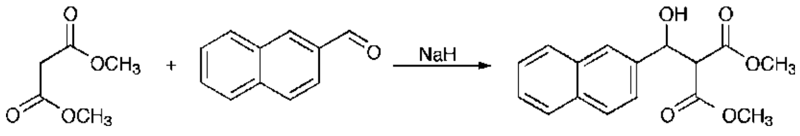
This molecule is composed of three fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to 2-naphthaldehyde, malonic acid, and methyl iodide.



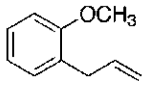
The combination of these compounds will generate the target compound through a two-step synthetic sequence. In the first step, illustrated below, malonic acid is converted to dimethyl malonate under mild basic conditions. This esterification reaction proceeds through an S_N2 reaction between a carboxylate anion and methyl iodide. The mechanism for an S_N2 reaction was presented in detail in Chapter 4. In this reaction it is important to use a base that is sufficient to deprotonate a carboxylic acid but not strong enough to remove a proton from the methylene group of malonic acid. Sodium bicarbonate is generally sufficient to affect this deprotonation. Please note that this same esterification can proceed under acidic conditions in methyl alcohol.



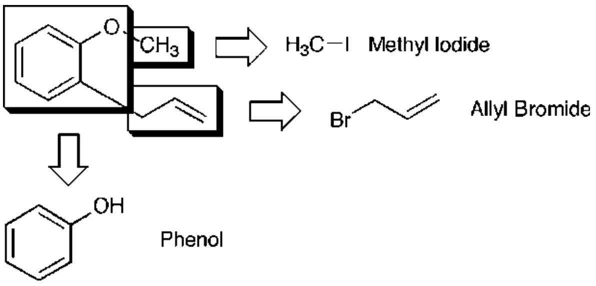
The second step in this sequence, illustrated below, is a 1,2-addition reaction between a dimethyl malonate anion and 2-naphthaldehyde. The mechanism for 1,2-addition reactions was discussed in detail in Chapter 7. In order for this reaction to proceed, it is important to use a base that is sufficient to deprotonate the methylene group of dimethyl malonate. Furthermore, it is important to use a base that will not hydrolyze the methyl esters. Sodium hydride is generally sufficient to affect this deprotonation.



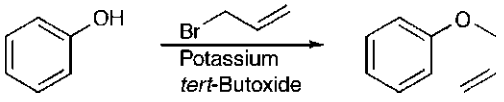
e.



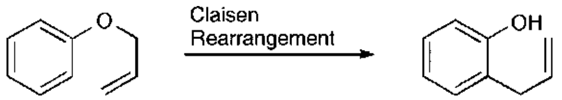
This molecule is composed of three fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to phenol (hydroxybenzene), allyl bromide, and methyl iodide.



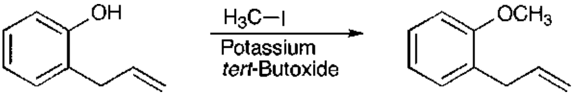
The combination of these compounds will generate the target compound through a three-step synthetic sequence. In the first step, illustrated below, phenol is alkylated with allyl bromide through an S_N2' mechanism. The mechanism for an S_N2' reaction was presented in detail in Chapter 4. In this reaction it is important to use a base that is sufficient to deprotonate a phenolic hydroxyl group. Potassium *tert*-butoxide is generally sufficient to affect this deprotonation.



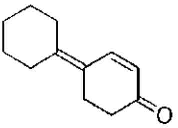
The second step of this sequence, illustrated below, is a Claisen rearrangement where the allyl group is migrated from the oxygen onto the aromatic ring. The mechanism for the Claisen rearrangement was presented in Problem 2(d) of this chapter.



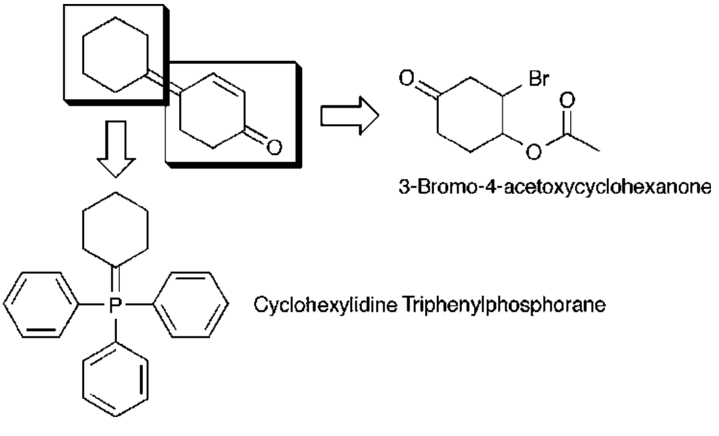
The third step of this sequence, illustrated below, is an S_N2 reaction between a phenol anion and methyl iodide. The mechanism for an S_N2 reaction was presented in detail in Chapter 4. In this reaction it is important to use a base that is sufficient to deprotonate a phenolic hydroxyl group. Potassium *tert*-butoxide is generally sufficient to affect this deprotonation.



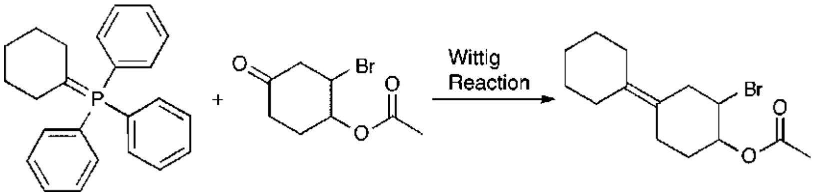
f.



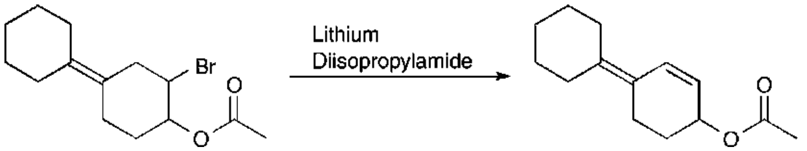
This molecule is composed of two fragments resembling structures from the above list of compounds. These fragments are illustrated below and relate to cyclohexylidine triphenylphosphorane and 3-bromo-4-acetoxycyclohexanone.



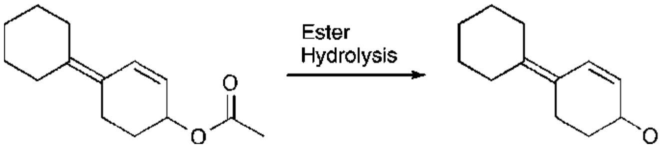
The combination of these compounds will generate the target compound through a four-step synthetic sequence. The first step, illustrated below, is a Wittig reaction between cyclohexylidine triphenylphosphorane and 3-bromo-4-acetoxycyclohexanone. The mechanism for the Wittig reaction was presented in Problem 2(a) of this chapter.



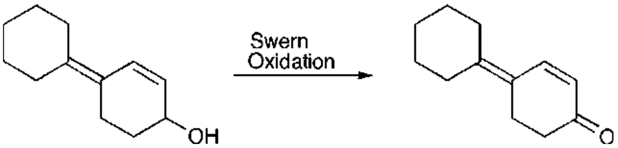
The second step of this sequence is an E2 elimination reaction generating a diene. The mechanism for an E2 elimination was presented in detail in Chapter 6. For this reaction to proceed, it is important to chose a base that is not nucleophilic and strong enough to remove an allylic proton. Lithium diisopropylamide is generally sufficient to affect this transformation.



The third step of this sequence, illustrated below, is an ester hydrolysis reaction. The mechanism for a base-mediated ester hydrolysis was highlighted in Scheme 7.19.



The fourth and final step of this sequence, illustrated below, is an oxidation of an alcohol to a ketone. This transformation can be accomplished utilizing the Swern oxidation. The mechanism for the Swern oxidation is shown in Problem 3(d) of this chapter.



Appendix 3

Student Reaction Glossary

The premise of this book is based on the presumption that introductory organic chemistry entails very little memorization. As presented in the chapters contained herein, this presumption is valid provided the student adheres to the philosophy that the study of organic chemistry can be reduced to the study of interactions between organic acids and bases. At this point, use of the principles presented in this book, in conjunction with more detailed coursework, allows students a broader understanding of organic chemistry reactions as described using combinations of fundamental organic mechanistic subtypes.

The mechanistic subtypes presented throughout this book include those related to the acid–base properties of organic molecules. These are protonations, deprotonations, and proton transfers. Mechanistic types based on solvation effects include solvolysis reactions, S_N1, and E1 processes. Additional mechanisms utilizing ionic interactions include S_N2, S_N2', E2, 1,2-additions, 1,4-additions, and addition–elimination processes. Finally, those mechanistic types dependent upon the presence of cationic species include alkyl shifts and hydride shifts.

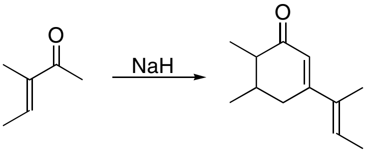
On the following pages, forms are provided that are designed to aid students in summarizing the various mechanistic components of reactions presented during introductory organic chemistry coursework. The forms are designed to allow students to summarize the name of a reaction in conjunction with its flow from starting material to product and its mechanism. To aid in the description of a reaction's mechanism, mechanistic subtypes are listed at the bottom of the table. Additional spaces are provided for students to add in more advanced mechanistic components presented throughout the subject.

As an example, the first form is filled out using the Robinson annulation. In completing this example, each mechanistic step was numbered in order to relate the appropriate mechanistic subtype to those listed in the form. Following this format, students are encouraged to complete additional pages using the reactions described in this book. Students are then encouraged to continue using these forms as an aid in the study of mechanistic organic chemistry.

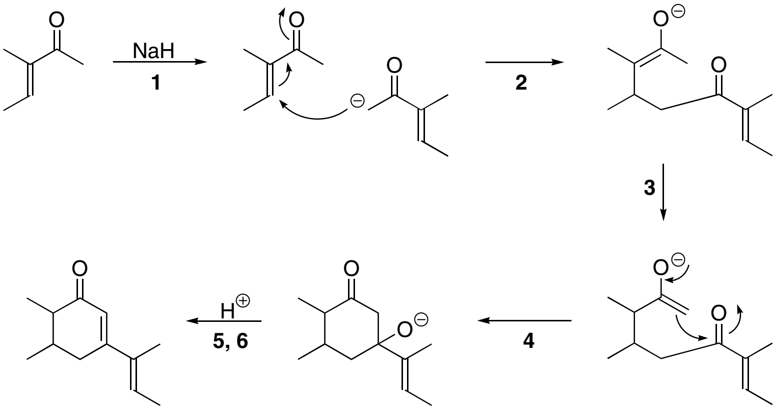
Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms.
By Daniel E. Levy

Reaction Name: Robinson Annulation	Homolytic ☐ Heterolytic ☑ Concerted ☐

Summary:



Mechanism:



Mechanistic Types	*Mechanism Steps*	*Mechanistic Types*	*Mechanism Steps*	*Mechanistic Types*	*Mechanism Steps*
Deprotonation	1	S_N2		Hydride shift	
Protonation	5	S_N2'		Alkyl shift	
Solvolysis		E1	6	1,2-Addition	4
Proton transfer	3	E2		1,4-Addition	2
S_N1		Addition–elimination			

Reaction Name:

Homolytic ☐
Heterolytic ☐
Concerted ☐

Summary:

Mechanism:

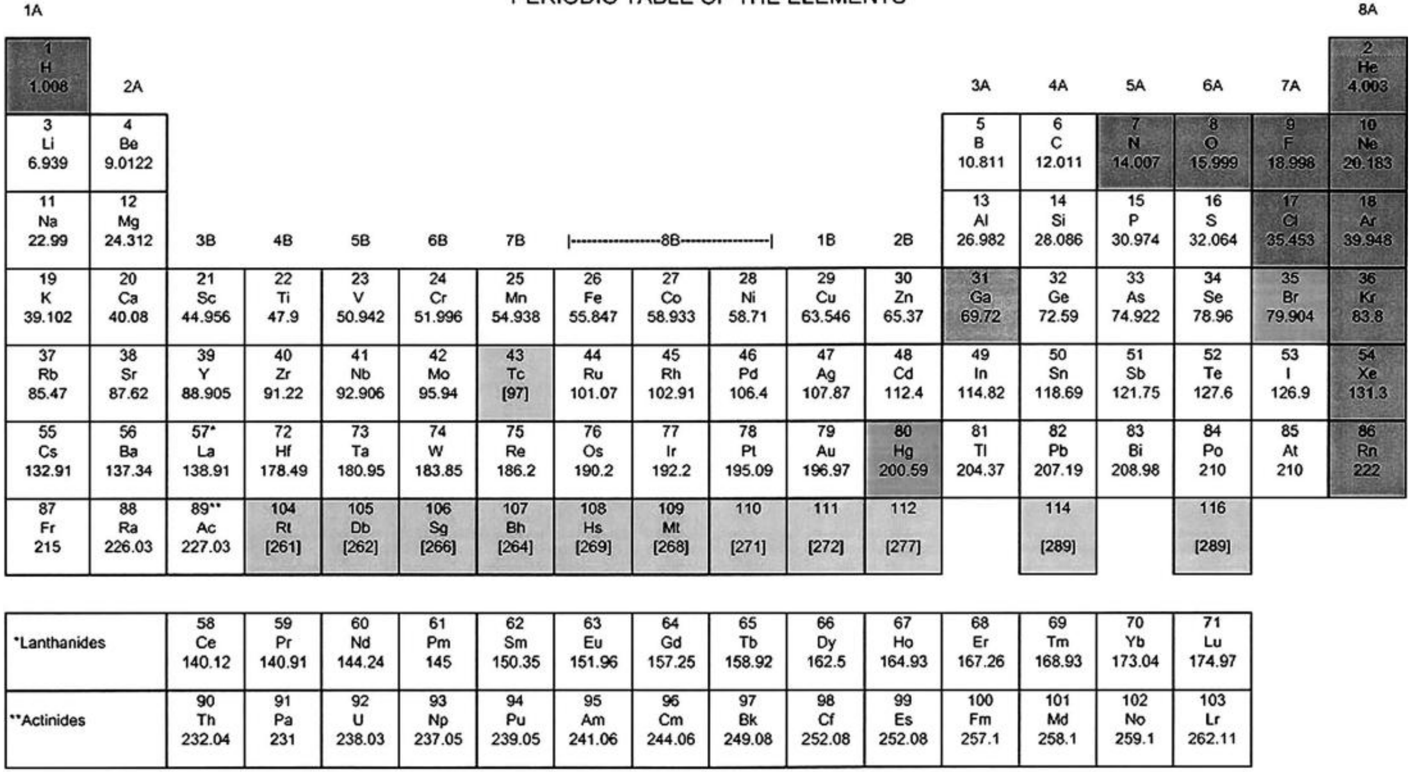
Mechanistic Types	*Mechanism Steps*	*Mechanistic Types*	*Mechanism Steps*	*Mechanistic Types*	*Mechanism Steps*
Deprotonation		S_N2		Hydride shift	
Protonation		S_N2'		Alkyl shift	
Solvolysis		E1		1,2-Addition	
Proton transfer		E2		1,4-Addition	
S_N1		Addition–elimination			

*This page may be reproduced as necessary.

Index

Arrow Pushing in Organic Chemistry: An Easy Approach to Understanding Reaction Mechanisms. By Daniel E. Levy

PERIODIC TABLE OF THE ELEMENTS



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1 H 1.008																	2 He 4.003
3 Li 6.939	4 Be 9.0122											5 B 10.811	6 C 12.011	7 N 14.007	8 O 15.999	9 F 18.998	10 Ne 20.183
11 Na 22.99	12 Mg 24.312											13 Al 26.982	14 Si 28.086	15 P 30.974	16 S 32.064	17 Cl 35.453	18 Ar 39.948
19 K 39.102	20 Ca 40.08	21 Sc 44.956	22 Ti 47.9	23 V 50.942	24 Cr 51.996	25 Mn 54.938	26 Fe 55.847	27 Co 58.933	28 Ni 58.71	29 Cu 63.546	30 Zn 65.37	31 Ga 69.72	32 Ge 72.59	33 As 74.922	34 Se 78.96	35 Br 79.904	36 Kr 83.8
37 Rb 85.47	38 Sr 87.62	39 Y 88.905	40 Zr 91.22	41 Nb 92.906	42 Mo 95.94	43 Tc [97]	44 Ru 101.07	45 Rh 102.91	46 Pd 106.4	47 Ag 107.87	48 Cd 112.4	49 In 114.82	50 Sn 118.69	51 Sb 121.75	52 Te 127.6	53 I 126.9	54 Xe 131.3
55 Cs 132.91	56 Ba 137.34	57* La 138.91	72 Hf 178.49	73 Ta 180.95	74 W 183.85	75 Re 186.2	76 Os 190.2	77 Ir 192.2	78 Pt 195.09	79 Au 196.97	80 Hg 200.59	81 Tl 204.37	82 Pb 207.19	83 Bi 208.98	84 Po 210	85 At 210	86 Rn 222
87 Fr 215	88 Ra 226.03	89** Ac 227.03	104 Rt [261]	105 Db [262]	106 Sg [266]	107 Bh [264]	108 Hs [269]	109 Mt [268]	110 [271]	111 [272]	112 [277]		114 [289]		116 [289]		

*Lanthanides	58 Ce 140.12	59 Pr 140.91	60 Nd 144.24	61 Pm 145	62 Sm 150.35	63 Eu 151.96	64 Gd 157.25	65 Tb 158.92	66 Dy 162.5	67 Ho 164.93	68 Er 167.26	69 Tm 168.93	70 Yb 173.04	71 Lu 174.97
**Actinides	90 Th 232.04	91 Pa 231	92 U 238.03	93 Np 237.05	94 Pu 239.05	95 Am 241.06	96 Cm 244.06	97 Bk 249.08	98 Cf 252.08	99 Es 252.08	100 Fm 257.1	101 Md 258.1	102 No 259.1	103 Lr 262.11

█ Gaseous at room temperature
▓ Liquid at room temperature
▒ Gallium mr elts at 29.78 °C
░ Synthetic elements
All other elements are solid at room temperature