19

Organic reaction mechanisms

Answers to worked examples

WE 19.1 Breaking bonds to form ions or radicals (on p. 869 in *Chemistry*^{3})

Use curly arrows to show the products formed on (a) heterolysis and (b) homolysis of the C–Br bond in Me_3C–Br.

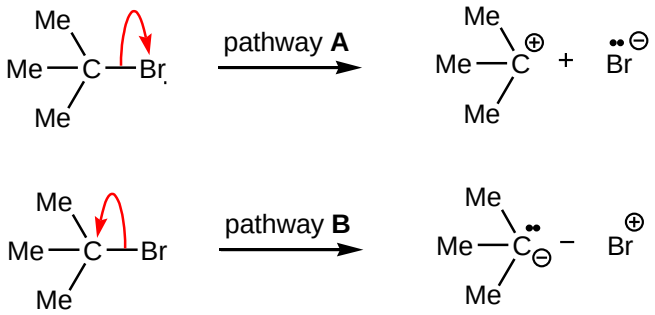
Strategy

Using a "double-headed" arrow symbolises the movement of a pair of electrons. By comparison, a "single-headed" arrow symbolises the movement of a single electron. Heterolytic cleavage of a bond involves unsymmetrical fragmentation to give an anion and a cation, and homolytic cleavage involves symmetrical fragment to give two radicals.

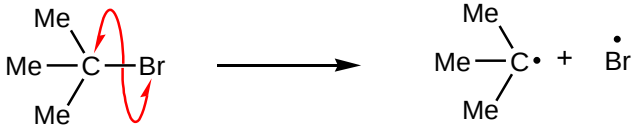
(a) Unsymmetrical heterolytic cleavage of an unsymmetrical bond, C-Br, has two different pathways. The more favour pathway will lead to the more stable cation and anion.
(b) Symmetrical homolytic cleavage of an unsymmetrical bond, C-Br, has one pathway.

Solution

(a) There are two potential pathways, **A** and **B**, for unsymmetrical heterolytic cleavage of this unsymmetrical C-Br bond. Pathway **A** is more favoured as it leads to the formation of a relative stable tertiary carbocation (Me_3C^+) and a stable bromide (Br^-) anion. Pathway **B** is disfavoured as it leads to an unstable carbanion and a bromonium ion. The curly arrow starts at the centre of the C-Br bond (where the pair of sigma electrons resides) and the "double-headed" arrow ends at the chosen atom.

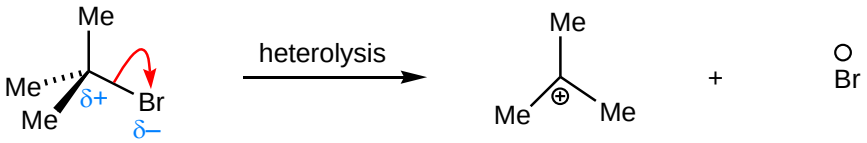


(b) Symmetrical homolytic cleavage of this unsymmetrical C-Br bond leads to two radicals, Me_3C▪ and Br▪. There are two "single-headed" curly arrows, which start at the centre of this C-Br bond (one for each electron present in its sigma bond) and each "single-headed" arrow ends at each atom of this bond.

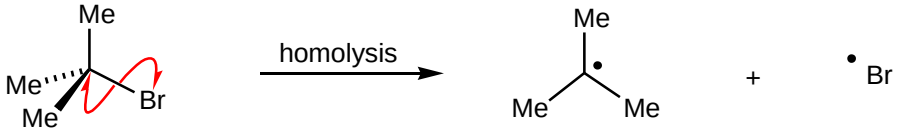


Answer

(a)



(b)



WE 19.2 Drawing resonance forms of carbocations (on p. 876 in *Chemistry*^{3})

By considering mesomeric effects, explain why $PhCH{=}CHCH_2^+$ is a more stable carbocation than $CH_3CH{=}CHCH_2^+$.

Strategy

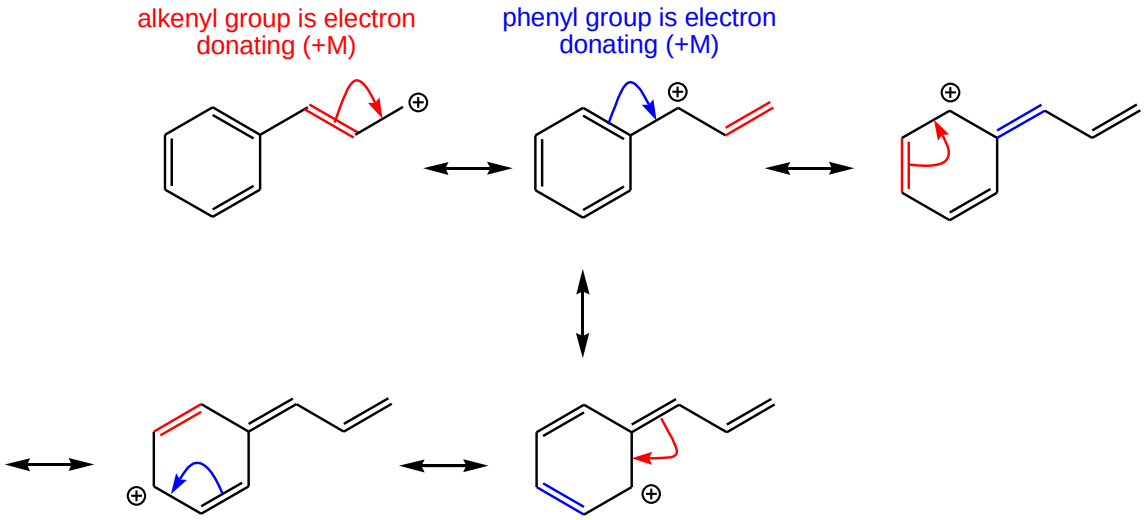
A mesomeric effect involves the movement of pi- and non-bonded electrons through pi-bonds. The more stable carbocation must have greater charge delocalisation.

Draw out the structures of $PhCH{=}CHCH_2^+$ and $CH_3CH{=}CHCH_2^+$. Ensure that the phenyl (Ph-) group is drawn out fully. Remember that the positively charged carbon atom is a

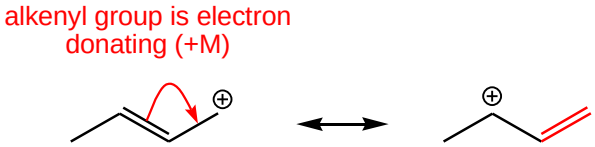
carbon atom that has 6 electrons and an empty 2*p*-atomic orbital, and therefore the curly arrows will move towards this positive charge.

Solution

$PhCH{=}CHCH_2^+$ is more stable than $CH_3CH{=}CHCH_2^+$ because of the extra resonance stabilisation from the neighbouring phenyl (Ph-) ring. Overall, FIVE resonance hybrids (or canonical structures) can be drawn for $PhCH{=}CHCH_2^+$. These are shown below:

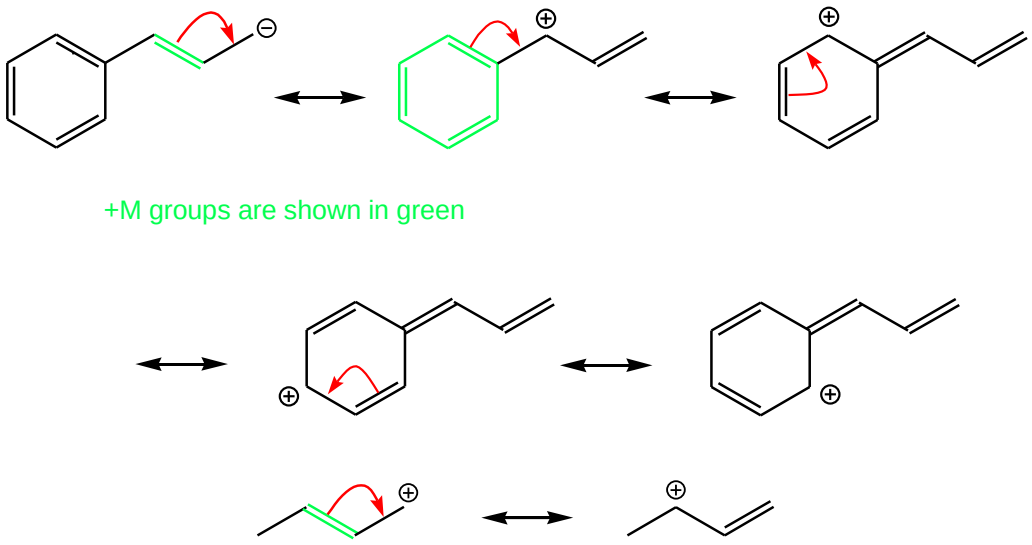


Whereas, for $CH_3CH{=}CHCH_2^+$, only two resonance hybrids (or canonical structures) can be drawn:



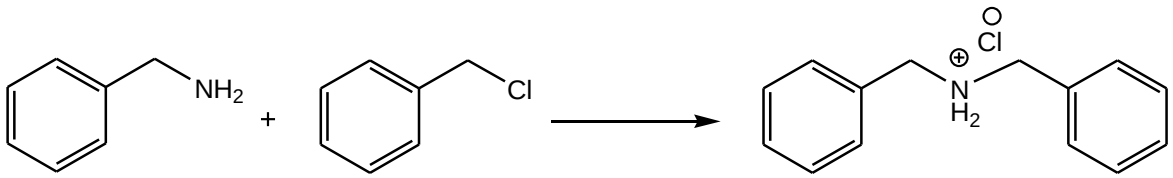
Answer

More resonance forms can be drawn for $PhCH{=}CHCH_2^+$ because the positive charge can be delocalised around the benzene ring.



WE 19.3 Spotting nucleophiles and electrophiles (on p. 883 in *Chemistry*[3])

(a) In the following reaction, which reactant is the nucleophile and which is the electrophile?



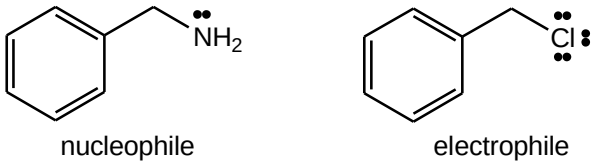
Strategy

A nucleophile is a reagent, which reacts with an electrophile, to form a covalent bond by donating its pair of non-bonding electrons. This nucleophile MUST have a pair of electrons to donate, and this electrophile MUST have an empty orbital to accept them.

Draw out both reagents and include any non-bonded pairs of electrons.

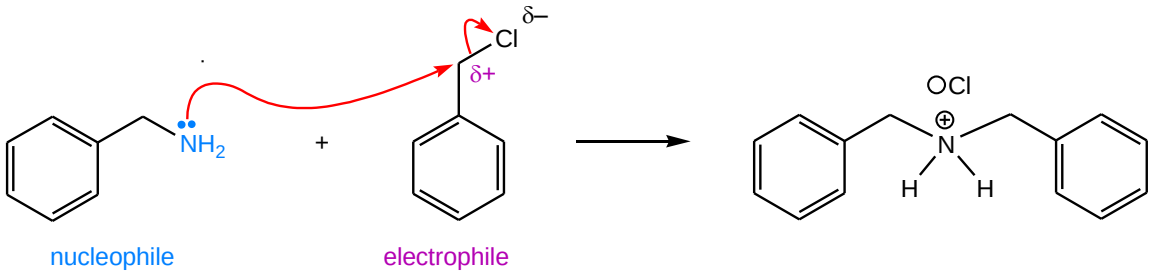
Solution

Benzyl amine is the nucleophile as it forms a covalent C-N bond by donating its pair of non-bonded electrons. Therefore, benzyl chloride is the electrophile in this reaction (even though it does contain three non-bonded pairs of electrons on its chlorine atom).



(b) Use curly arrows to show the mechanism of the reaction and draw the product that is formed.

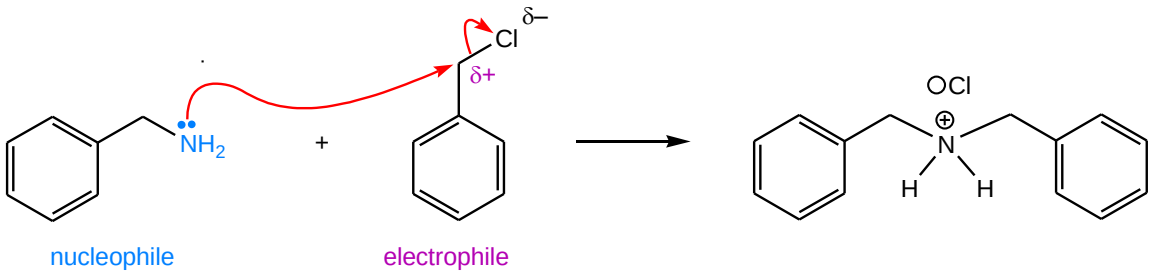
The first curly arrow, a, starts at the non-bonded pair of electrons on the nitrogen atom of the nucleophile, benzyl amine, and ends at the carbon atom of the electrophile, benzyl chloride to form the blue C-N bond.



As this curly arrow involves the movement of a pair of electrons it has a "double-headed" arrow. Simultaneously, a second curly arrow, b, is needed to prevent the carbon atom of this electrophile from having 10 valence electrons. This "double-headed" curly arrow symbolises the heterolytic cleavage of the C-Cl bond to give a chloride anion; the curly arrow starts in the centre of this C-Cl bond, where the two sigma electrons resides, and ends on the chlorine atom, to give the chloride, Cl^-, anion

Answer

(a) and (b)



WE 19.4 Comparing the strengths of bases (on p. 898 in *Chemistry*[3])

DMAP [(4-dimethylamino)pyridine] is another useful base in organic synthesis.

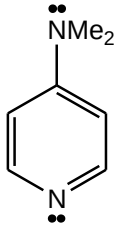
(a) Draw the structure of the more stable conjugate acid of DMAP.

Strategy

1. Draw out the structure of (4-dimethylamino)pyridine and include any non-bonded pairs of electrons.
2. Draw out all potential conjugate acids and consider their relative stability. [Remember, the more stable the conjugate acid, the more basic the nitrogen atom.]
3. Draw out the structure of the more stable conjugate acid and give your reasons why.

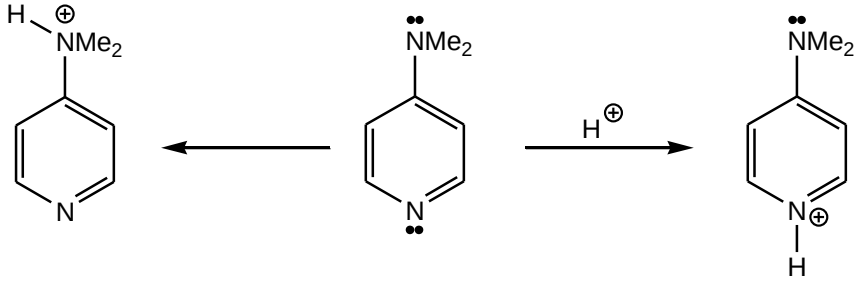
Solution

1. (4-Dimethylamino)pyridine has two non-bonded pairs of electrons, one pair on each nitrogen atom. Its structure is shown below.



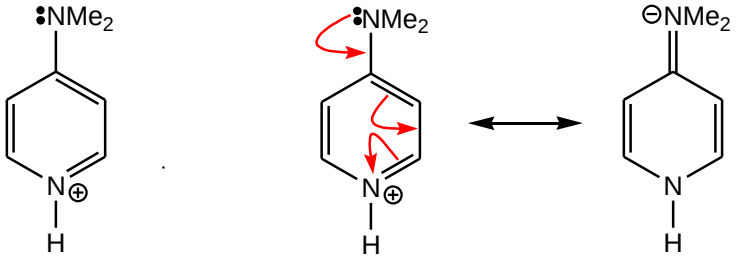
(4-dimethylamino)pyridine

2. Protonation of each nitrogen atom [of 4-dimethylamino)pyridine] leads to two conjugate acids, **A** and **B**. The structures of these conjugate acids are shown below.



A **B**

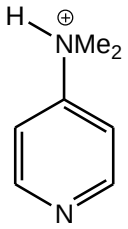
3. Conjugate acid **B** is more stable than conjugate acid **A** due to resonance stabilisation; the 4-dimethylamino (Me_2N-) group is able to stabilise the positive charge on the bottom nitrogen atom by donating its non-bonded electrons through the pyridinium ring. This movement of electrons is shown below. The ammonium ion in conjugate acid **A** cannot be stabilised through resonance; try and draw a few resonance structures to convince yourself that this is the case.



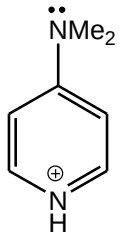
B

Answer

most stable conjugate acid



protonation of the sp^3 nitrogen of DMAP gives a conjugate acid that cannot be stabilised by resonance



protonation of the sp^2 nitrogen gives a conjugate acid that can be stabilised by resonance

(b) By comparing the stability of the conjugate acids of DMAP and pyridine, explain why DMAP is the stronger base

Strategy

You already know the structure of preferred conjugate acid of DMAP from your answer above.

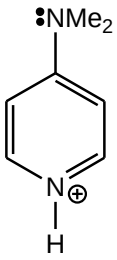
With all things being equal, the stronger base will have a weaker and more stable conjugate acid.

Draw out both conjugate acids of DMAP and pyridine and consider their relative stability.

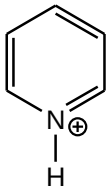
Solution

The conjugate acids of DMAP and pyridine are shown below. The conjugate acid of DMAP is more stable than that of pyridine due to resonance stabilisation; its 4-dimethylamino (Me_2N-) group is able to stabilise the positive charge on the bottom nitrogen atom by donating its non-bonded electrons through the pyridinium ring.

For the conjugate acid of pyridine, there is no additional resonance stabilisation as there is no substituent present to aid stabilisation.



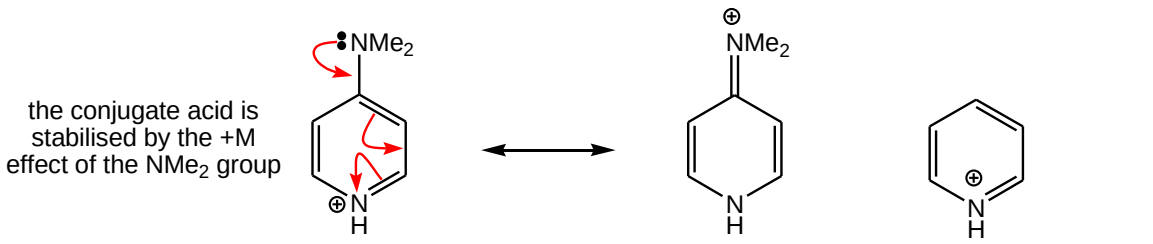
conjugate acid of (4-dimethylamino)pyridine



conjugate acid of pyridine

Answer

conjugate acid of DMAP



the conjugate acid of DMAP is more stable than the conjugate acid of pyridine because of the additional +M effect of the NMe_2 group

the conjugate acid of pyridine is not stabilised by resonance

WE 19.5 Assigning oxidation levels (on p. 901 in *Chemistry*[3])

Assign oxidation levels to the carbon atoms in **A**–**C**. Use these values to determine if the transformations of **A** → **B** and **B** → **C** involve oxidation, or reduction, or neither.

Strategy

To answer this question, you will need to work out if the oxidation level of each carbon atom has increased, decreased or stayed the same during these reactions. If the oxidation number increases, then it is an oxidation, if it decreases, then it is a reduction, and if it

stays the same, it is neither. If you are unsure how to assign oxidation levels of organic compounds; see Table 19.2 on page 893 in *Chemistry*[3].

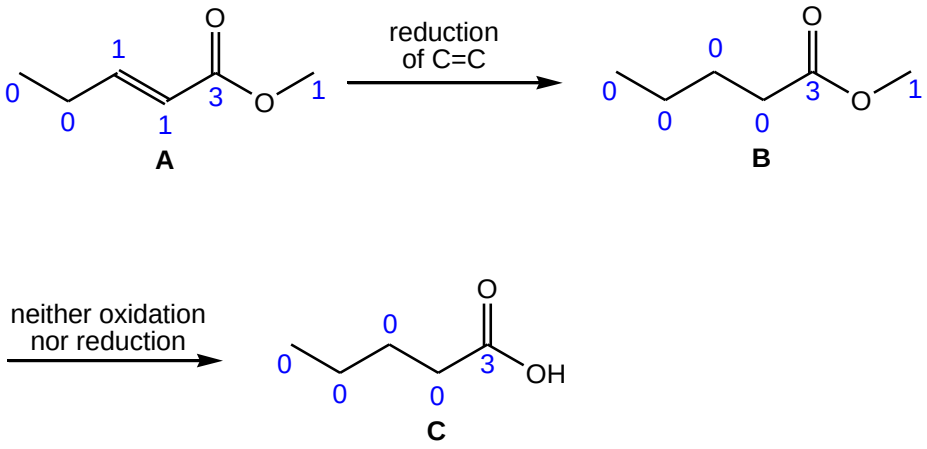
Solution

There are six carbon atoms in molecule **A**. The highest oxidation level, +3, is at the carbonyl group, and the lowest oxidation level, 0, is at the alkyl CH_3 and CH_2 groups.

For the conversion **A**→**B**, there is a decrease in the oxidation level of two carbon atoms in **A** from +1 to 0 (in **B**). Overall, this step involves a reduction at both carbon atoms of the alkene, in **A**, to give an alkane, in **B**.

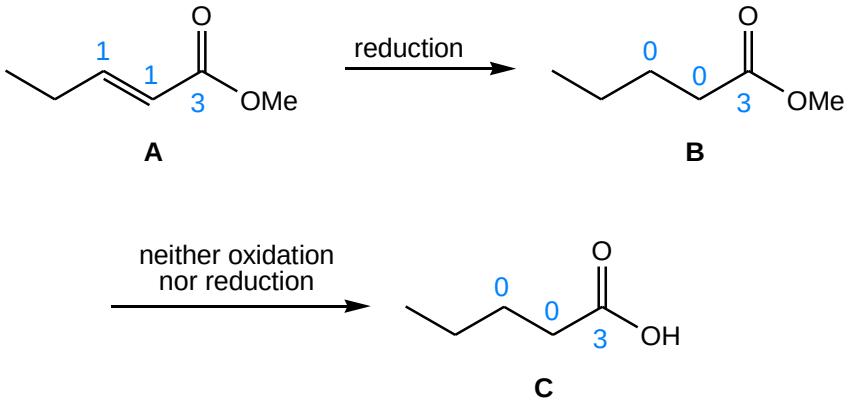
For the conversion **B**→**C**, there is no change in the oxidation levels of these molecules, so this transformation involves neither an oxidation nor a reduction.

Potential reagents for these conversions are Pd, H_2 (for **A**→**B**) and NaOH, H_2O (followed by an acidic work-up) (for **B**→**C**).



Answer

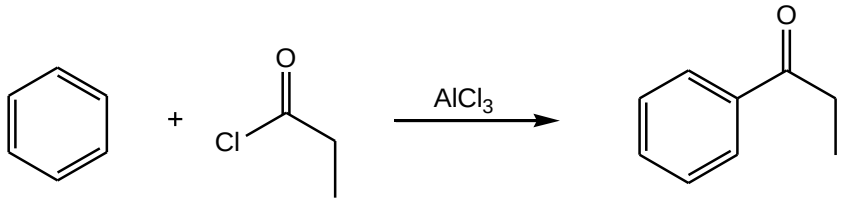
Only the important oxidation levels need to be shown.



WE 19.6 Classifying reactions (on p. 906 in *Chemistry*^{3})

Part of a racemic synthesis of the pain-relieving drug propoxyphene is shown on p. 903 in *Chemistry*^{3}.

(a) Compound **A** is prepared by reacting benzene with EtCOCl and $AlC1_3$. What type of reaction does this involve?



Strategy

The only way of deducing its reaction type is to know what type of reaction mechanism is involved.

Solution

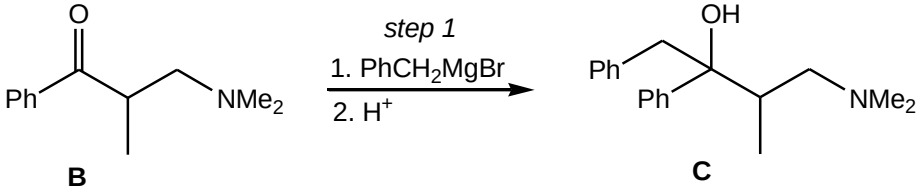
This reaction proceeds by **electrophilic addition** of benzene using the intermediate acylium ion $EtC{\equiv}O^+$ (derived from EtCOCl and $AlCl_3$) as the electrophile, followed by **elimination** of a proton gives the phenyl ketone **A**. Overall, this reaction involves **substitution** (C-H is replaced by C-COEt) and is **electrophilic** in origin.

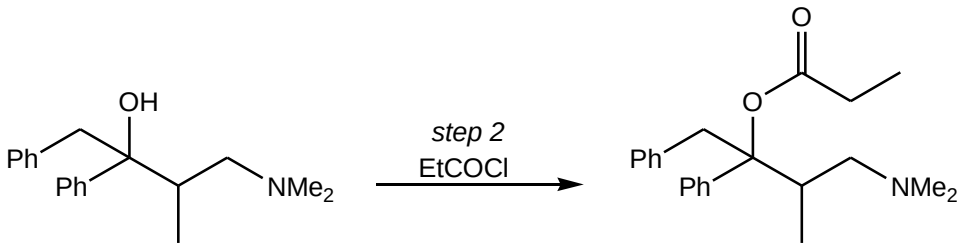
This reaction can be classed as an **electrophilic substitution** reaction.

Answer

An electrophilic substitution reaction.

(b) What types of reactions are taking place in steps 1 and 2?





C **D**

Strategy

In order to deduce these reaction types you need to know what type of reaction mechanisms are involved in these steps.

Solution

Step 1: This step involves **nucleophilic addition** of the Grignard reagent, $PhCH_2MgBr$, to the ketone group in **B**. Protonation of the intermediate magnesium alkoxide gives the tertiary alcohol in **C**. This reaction involves **nucleophilic addition**.

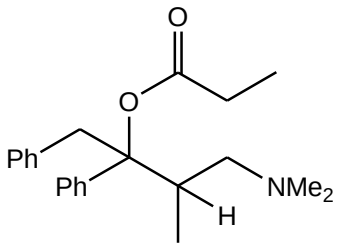
Step 2: This step involves the formation of an ester group, in **D**, derived from the corresponding tertiary alcohol, in **C**, and EtCOCl. **Nucleophilic addition** of this tertiary alcohol, in **D**, to the acid chloride, followed by **elimination** of chloride gives this ester group. Overall, this step involves **substitution** (from C-Cl to C-O) and is **nucleophilic** in origin. This reaction is classed as a **nucleophilic substitution** (or nucleophilic addition/elimination).

Answer

Step 1 – nucleophilic addition.

Step 2 – nucleophilic acyl substitution.

(c) Identify the chiral centres in propoxyphene and explain what is meant by a *racemic synthesis*. (*Hint*: see section 18.4 on p. 832 in *Chemistry*^{3}).



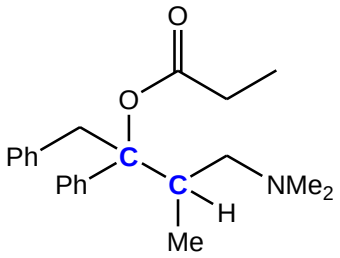
propoxyphene

Strategy

For an atom to be a chiral centre it must have four different substituents attached to it. Work out how many chiral centres there are in this molecule. It is worth while checking if there are any other elements of symmetry present (which will reduce this number).

Solution

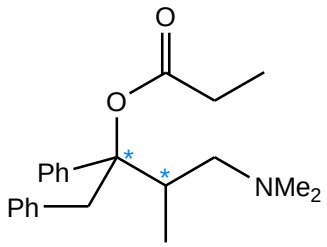
There are two chiral centres in this molecule; each is highlighted as a blue carbon atom, **C**. A racemic synthesis simply means that a racemic product is formed. As there are two chiral centres, this product will consist of a mixture of 4 stereoisomers; *i.e.*, there will be two diastereoisomers, and each one will have a pair of enantiomers. [Alternatively, there will be two pairs of enantiomers for both diastereoisomers.] There are no other elements of symmetry present.



propoxyphene

Answer

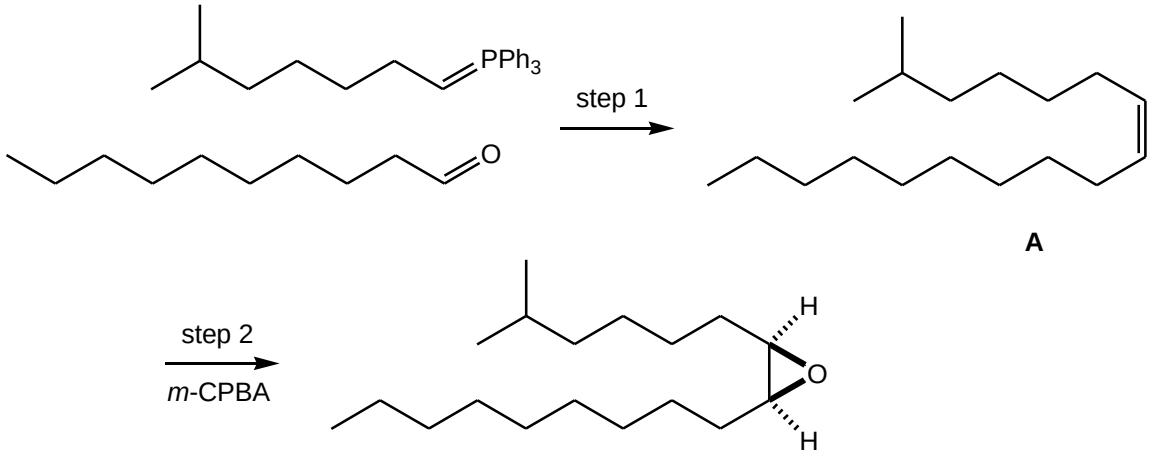
Propoxyphene is formed as a mixture of four enantiomers. None of the reactions used to prepare propoxyphene are enantiomer selective.



* = chiral centre
propoxyphene

WE 19.7 Selective reactions (on p. 911 in *Chemistry*^{3})

Disparlure is a natural pheromone produced by female gypsy moths to attract males for mating. A racemic synthesis is shown below.



Disparlure
(the relative configuration is shown)

(a) Explain why step is classed as a stereoselective reaction.

Strategy

For a step to be stereoselective, it must involve the formation of stereoisomers (stereo-) and it must be selective; *i.e.*, **stereoselective**. If there is a **choice** within its mechanism, then it will always be **selective**.

Solution

Step 1 is stereoselective because it has the potential to form both the *cis*- and *trans*-alkenes. It selectively forms the major *cis*-alkene **A** [or (*Z*)-alkene]; the minor *trans*-alkene [(*E*)-alkene] is not drawn.

Answer

Step 1 is stereoselective because it leads to the selective formation of an alkene with (*Z*)- rather than (*E*)-configuration.

(b) Why is step 2 classed as a stereospecific reaction?

Strategy

For a step to be stereospecific, it must involve the formation of a single stereoisomer and there is **no choice** within its mechanism.

Solution

Step 2 is stereospecific as this oxidation can only lead to one epoxide. The major *cis*-alkene **A** leads stereospecifically to the *syn*-epoxide (as drawn). Formation of the *anti*-epoxide is mechanistically impossible!

Answer

Step 2 is stereospecific because the (*Z*)-alkene forms the *cis*-epoxide. The corresponding (*E*)-alkene would form the corresponding *trans*-epoxide.

(c) Is step 2 an enantioselective or diastereoselective reaction?

Strategy

For a reaction to be enantio- or diastereoselective it must be capable of forming a mixture of enantiomers or diastereoisomers, respectively.

Solution

In this step, both enantiomers of disparlure are formed as epoxidation of the achiral alkene **A** occurs equally on both faces to give a racemic mixture; this process is not selective as it does not select over either enantiomer. This step cannot be diastereoselective as only the *syn*-epoxide can be formed. Step 2 is neither enantioselective nor diastereoselective; it is a **diastereospecific** reaction.

Answer

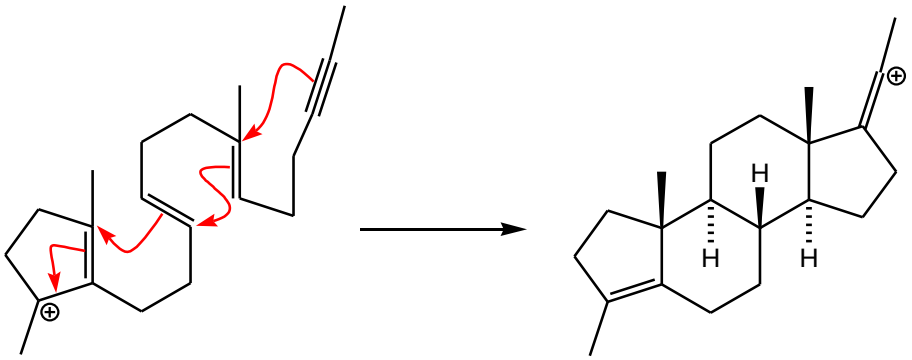
Step 2 is neither enantioselective nor diastereoselective. It is diastereospecific as only one diastereoisomer is formed. Reaction of this (Z)-alkene with the achiral peroxycarboxylic acid forms a racemic mixture of one diastereoisomeric epoxide.

Answers to boxes

Box 19.2 Natural cascades (on p. 864 in *Chemistry*[3])

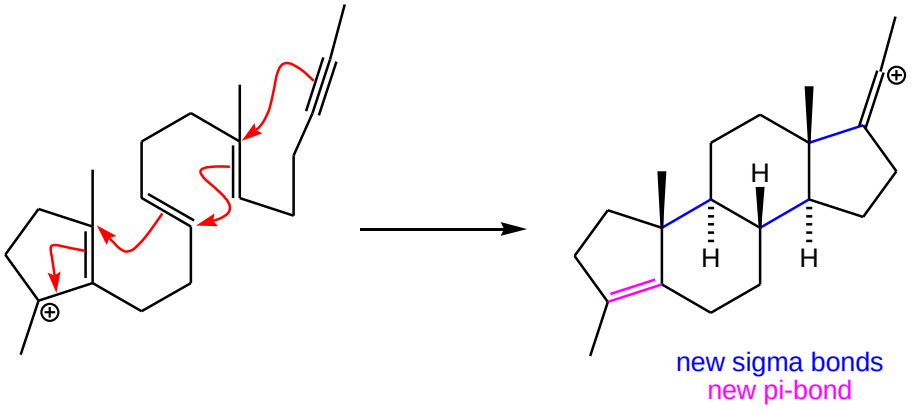
The occurrence of a cascade reaction (to form steroids) in nature has inspired researchers to mimic this type of reaction in the laboratory. This is called **biomimetic synthesis**. An example of a biomimetic cascade reaction, to form a similar ring system to that found in steroids, is shown here.

(a) Identify the new **sigma**-bonds that are formed in the cascade reaction.



Strategy

The easiest way to find where the new **sigma**-bonds have been formed, is to overlap the carbon skeletons of the starting material and the product.

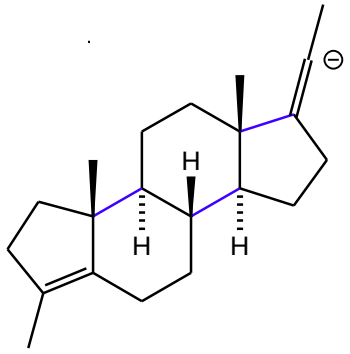


Solution

By overlapping carbon skeletons of the starting material and the product, it is obvious that there are three new sigma bonds and one new pi-bond formed. The total number of new bonds formed generally equals the number of curly arrows drawn (as each arrow symbolises a pair of electrons).

Answer

(a)



three new sigma bonds

(b) Identify the chiral centres in the product, and draw its enantiomer.

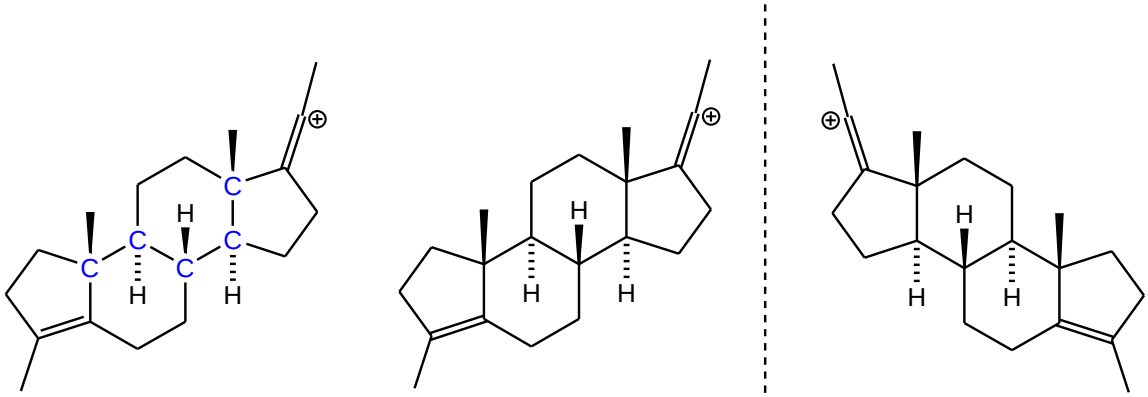
Strategy

For an atom to be a chiral centre it must have four different substituents attached to it. Work out how many chiral centres there are in this molecule. It is worth while checking if there are any other elements of symmetry present (which will reduce this number).

As enantiomers are non-superimposable mirror images of each other, the enantiomer of this product will simply be its mirror image.

Solution

There are five chiral centres in this molecule; each is highlighted as a blue carbon atom, C. There are no other elements of symmetry present. The enantiomer of this product is simply its mirror image (which is non-superimposable).



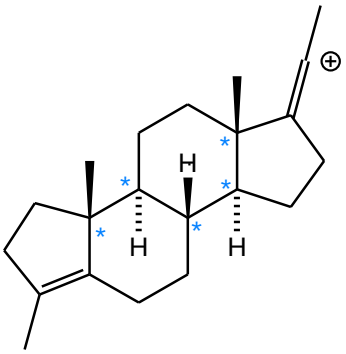
five chiral centres

original structure

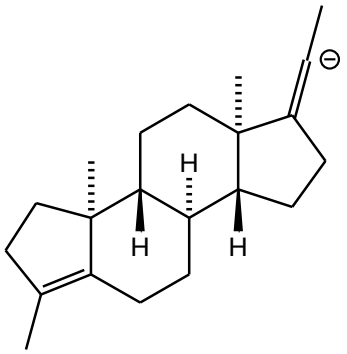
mirror plane

enantiomer of the original structure

Answer



* = chiral centre



the enantiomer of the product

Box 19.3 George Olah and carbocations (on p. 868 in *Chemistry*[3])

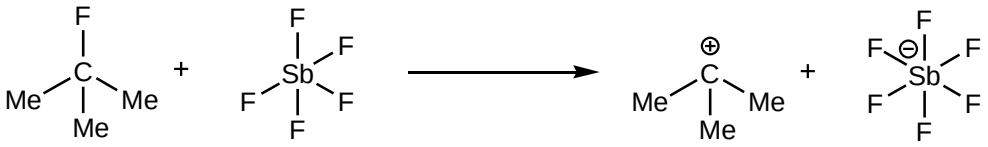
One of Olah's early and successful experiments to form carbocations involved treating 2-fluoro-2-methylpropane with SbF_5 at low temperature. Suggest a balanced equation for this reaction.

Strategy

Draw out the chemical structure of 2-fluoro-2-methylpropane and the reagent SbF_5. In order to form a carbocation, a fluoride anion must be lost from 2-fluoro-2-methylpropane.

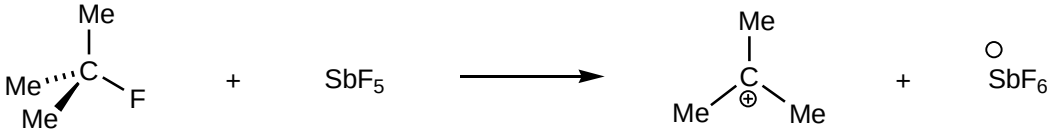
Solution

This reaction involves the transfer of fluoride from 2-fluoro-2-methylpropane to antimony pentafluoride (SbF_5) to give a tertiary carbocation, Me_3C^+, and antimony hexafluoride, SbF_6^-. The balanced chemical equation is given below.



2-fluoro-2-methylpropane

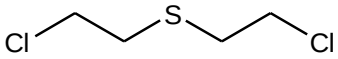
Answer



tert-butyl cation

Box 19.4 Anti-cancer agents (on p. 883 in *Chemistry*[3])

Mustard gas is a chemical warfare agent, first used in World War 1, which stops cell division by cross-linking DNA. Propose a mechanism to show how mustard gas is able to cross-link DNA.

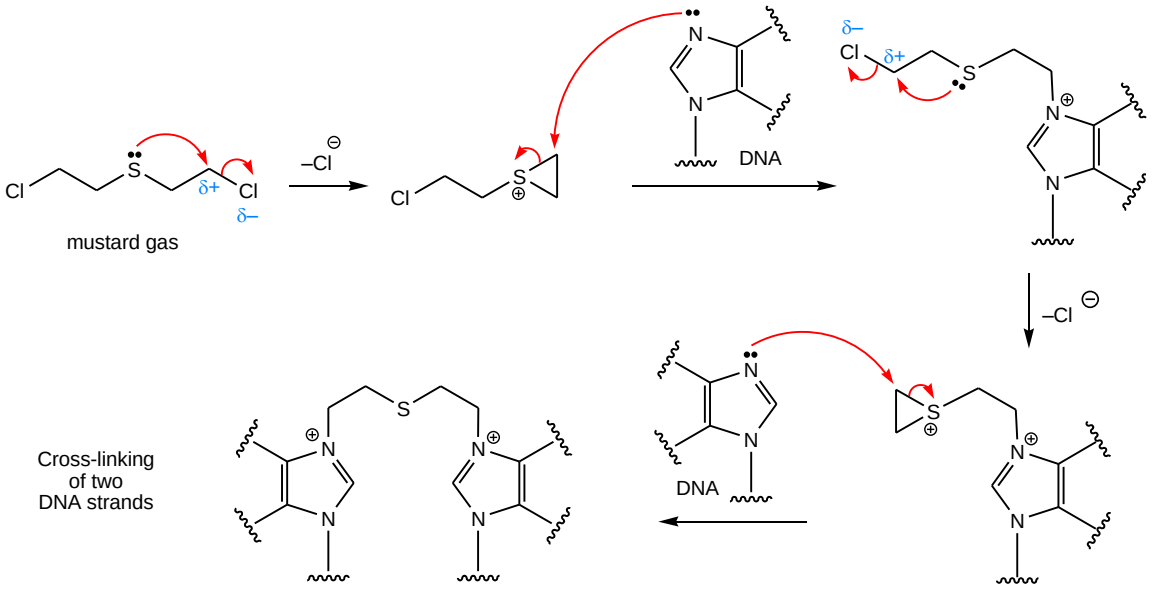


mustard gas

Strategy

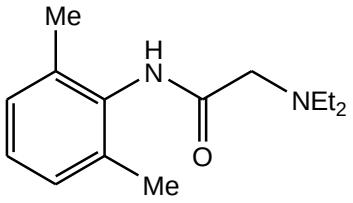
Review the mechanism given for the nitrogen mustard, mechlorethanmine, which is outlined in box 19.4 on p. 877 in *Chemistry*[3]. Replace the methylamino (-NMe-) group in mechlorethanmine for a sulfanyl (-S-) group, and repeat the same mechanism. Note that sulfur has TWO non-bonded pairs of electrons in which only ONE of these are used.

Solution/Answer

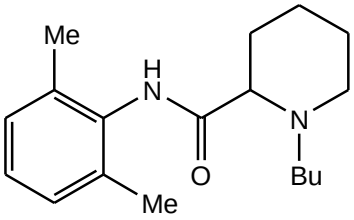


Box 19.5 Natural acids and bases (on p. 894 in *Chemistry*[3])

(a) Suggest an explanation for why bupivacaine (the pK_a of the conjugate acid is 8.1) is a slower acting local anaesthetic than lignocaine.



lignocaine



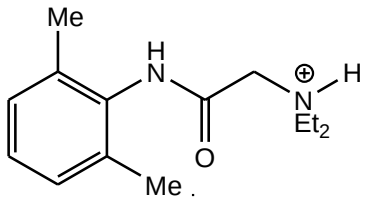
bupivacaine

Strategy

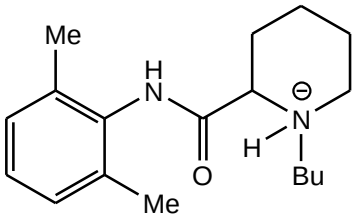
The more basic "caine" will be the slower acting local anaesthetic, as its conjugate acid (an ammonium ion) is unable to pass through the hydrophobic fat-soluble layer, which surrounds the nerve cells.

Solution

The conjugate acid of bupivacaine (pK_a 8.1) is less acidic than that of lignocaine (pK_a 7.7); therefore bupivacaine is more basic than lignocaine. The slower acting local anaesthetic is bupivacaine.



conjugate acid of lignocaine
pK_a = 7.7



conjugate acid of bupivacaine
pK_a = 8.1

Answer

The conjugate acid of bupivacaine (pK_a 8.1) has a higher pK_a value than the conjugate acid of lignocaine (pK_a 7.7). At physiological pH (7.4), more molecules of bupivacaine will be protonated and so they are not able to pass through the fat-soluble layer that surrounds the nerve cells.

(b) Draw the structure of the conjugate acid of bupivacaine

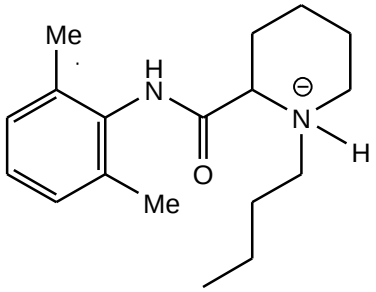
Strategy

There are two nitrogen atoms in this molecule; one is part of the tertiary amine (-NBu-) group and the other is part of the amide (-CONH-) group. Which one of these is more basic?

Solution

The nitrogen atom of the amide group is less basic than the tertiary amine because its non-bonded pair of electrons are stabilised through conjugation with its neighbouring carbonyl group. The more basic tertiary amine will be preferentially protonated.

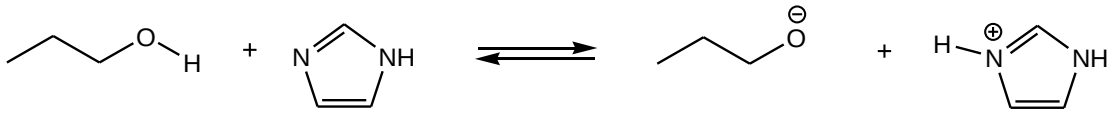
Answer



a tertiary amine is more basic than an amide

Box 19.6 Natural acid–base catalysis (on p. 897 in *Chemistry*[3])

In step 1, in the above mechanism, chymotrypsin produces an alkoxide ion by deprotonation of an alcohol using an imidazole group as the base. In the absence of the enzyme, where would you expect the equilibrium of the reaction of ethanol with imidazole to lie?



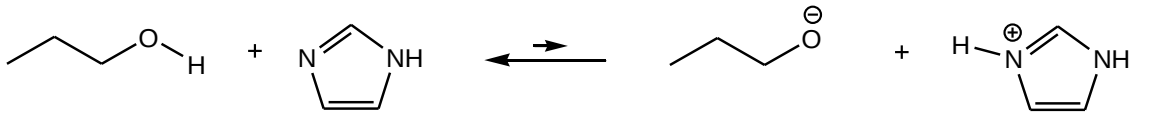
ethanol pK_a (16) | imidazole | ethoxide | imidazolium ion pK_a (7)

Strategy

Examine the pK_a values for both acids. The equilibrium will favour the more stable (and less acidic) acid.

Solution

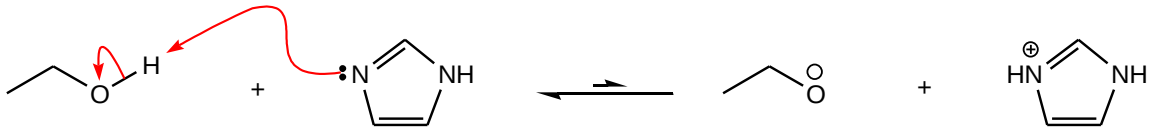
Ethanol (pK_a 16) is less acidic than the imidazolium ion (pK_a 7), and therefore the equilibrium will favour the left-hand side of this equilibrium (the ethanol side). Also, ethoxide is more basic than imidazole, so the overall equilibrium favours the left-hand side as shown below:



weaker acid weaker base stronger base stronger acid

Answer

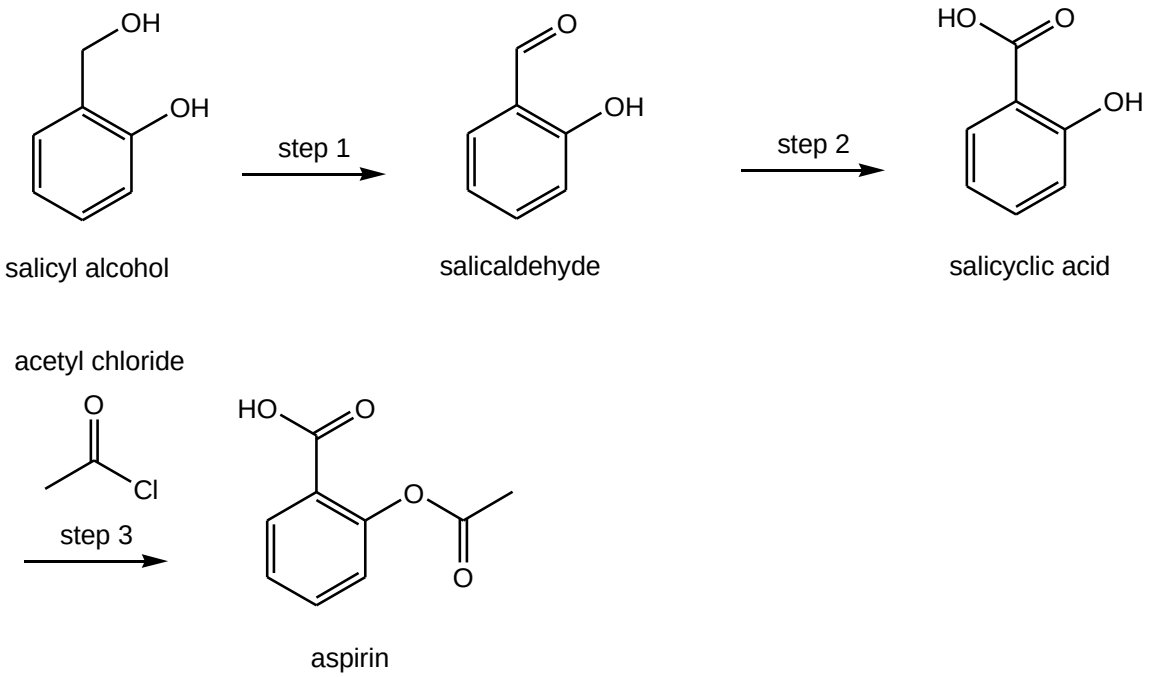
The conjugate acid of imidazole has a lower pK_a than ethanol, and therefore has a greater tendency to donate a proton. The equilibrium will lie to the left-hand side.



pK_a 16–17 pK_a 7

Box 19.7 Aspirin (on p. 900 in *Chemistry*[3])

Salicin, isolated from the willow tree, reacts with water (hydrolysis) to form salicyl alcohol and glucose. The conversion of salicyl alcohol into aspirin involves the three steps shown below. Salicylic acid is converted into aspirin using acetyl chloride (CH_3COCl). Assign oxidation levels to the carbon atoms in acetyl chloride and to each of the four molecules in the following reaction schemes. Use your values to identify which steps involve redox reactions.

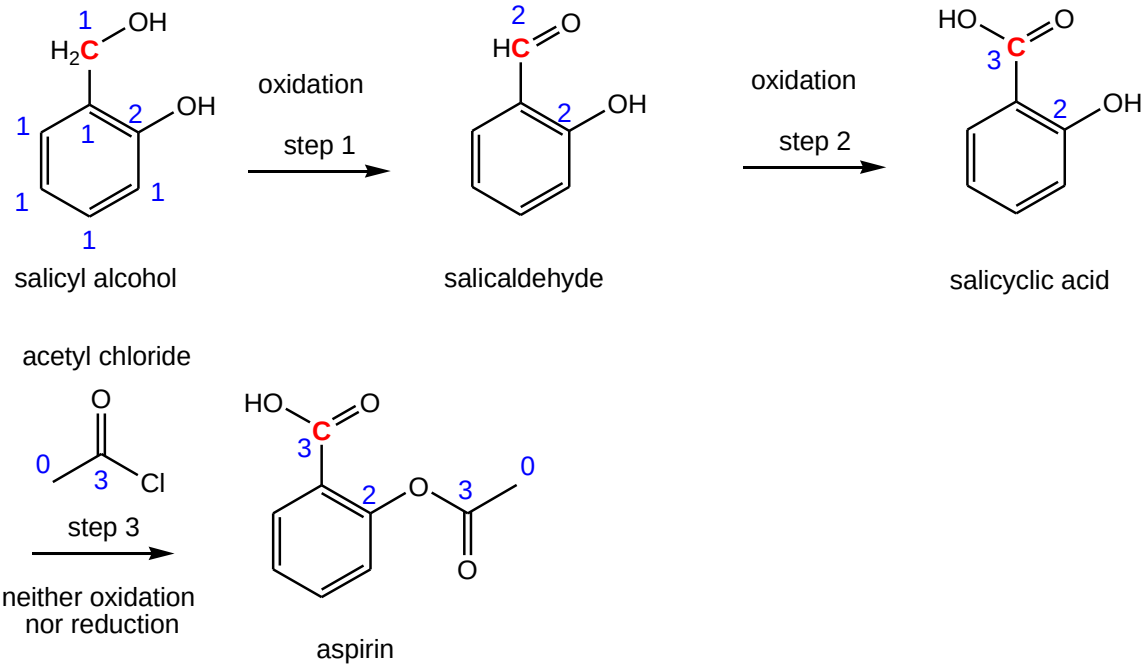


Strategy

To answer this question, you will need to work out if the oxidation level of each carbon atom has increased, decreased or stayed the same during these reactions. If the oxidation number increases, then it is an oxidation, if it decreases, then it is a reduction, and if it stays the same, it is neither. If you are unsure how to assign oxidation levels of organic compounds see Table 19.2 on page 893 in *Chemistry*[3].

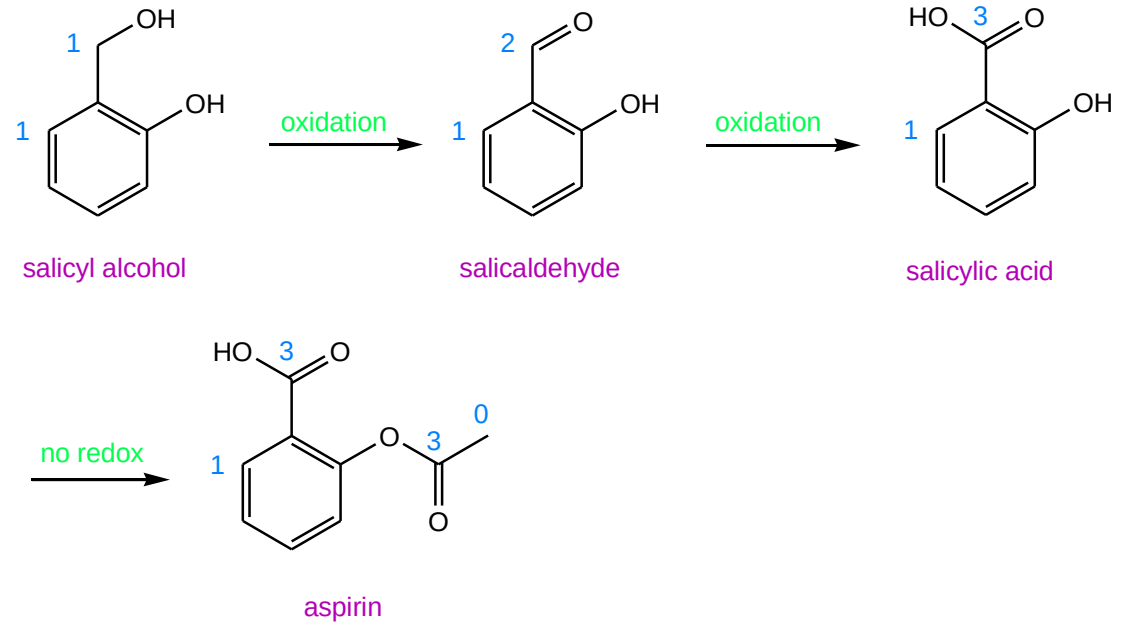
Solution

The important changes in oxidation numbers occur at the (red) carbon atom (of the primary alcohol) in salicyl alcohol; steps 1 and 2 involve oxidation at this position. Neither oxidation nor reduction occurs in step 3, as the oxidation levels in acetyl chloride remain unchanged.



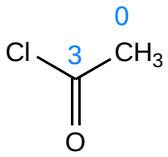
Answer

The blue numbers indicate oxidation levels in the reaction scheme below.



The first two steps involve oxidation reactions because the carbon atoms increase in oxidation level – from oxidation level 1 for the CH_2OH carbon in salicyl alcohol, to 2 for the aldehyde carbon in salicaldehyde, to 3 for the carboxylic acid carbon in salicylic acid.

The third step is not a redox reaction because the oxidation level of the carbonyl carbon in acetyl chloride does not change on reaction with salicylic acid. The oxidation levels of the carbon atoms in acetyl chloride are:



Box 19.8 Superglue and fingerprints (on p. 904 in *Chemistry*^{3})

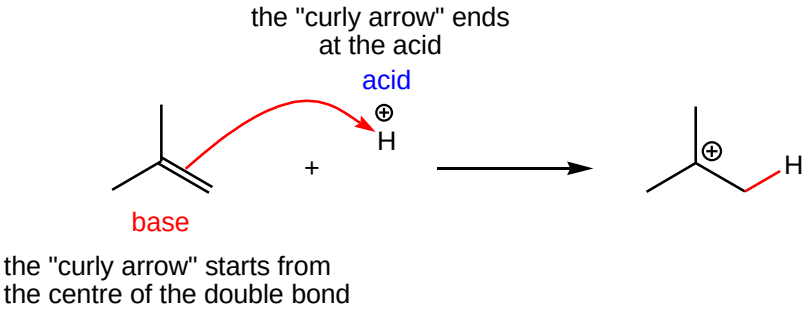
The polymerization of ethyl 2-cyanoacrylate by hydroxide ion is an example of an **anionic polymerization**. Alkenes also undergo polymerization by reaction mechanisms that involve radicals or carbocations. For example, the **cationic polymerization** of 2-methylpropene (isobutylene) can be promoted by the addition of a small amount of an acid as shown on p. 899 in *Chemistry*^{3}.

(a) Use a curly arrow to show the mechanism of step 1.

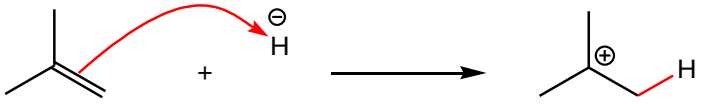
Strategy

H^+ contains no electrons, and therefore the curly arrow must start at the centre of the pi-bond of this alkene, where the two pi-electrons reside. As this alkene is unsymmetrical alkene, protonation can lead to two carbocations. Only the more stable and preferred tertiary carbocation is drawn in this question.

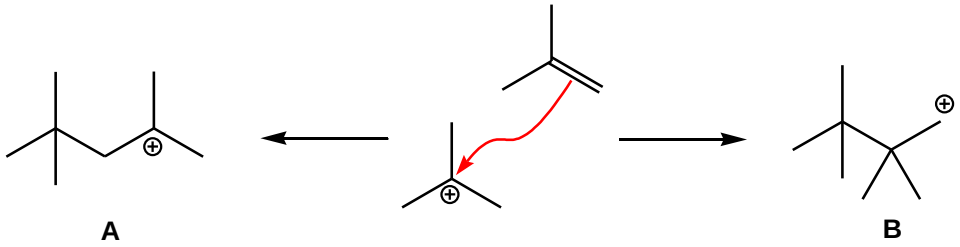
Solution



Answer



(b) Explain why carbocation **A** is formed in step 2, rather than carbocation **B** (formed by the mechanism shown below)



Strategy

Examine the structure of both carbocations, **A** and **B**. The **more** stable carbocation is generally the **more** preferred.

Solution

Carbocation **A** is the more stable and more substituted tertiary carbocation. This carbocation can be stabilised through hyperconjugation using its adjacent alkyl substituents. Carbocation **B** is the less stable and less substituted primary carbocation. This carbocation cannot be stabilised by hyperconjugation as there are **no** adjacent primary, secondary or tertiary alkyl substituents, which are capable of donating their alpha C-H bonds. For additional information about hyperconjugation, see p. 866 in *Chemistry*[3].

Answer

The reaction forms tertiary carbocation **A**, rather than primary carbocation **B**, because tertiary carbocation **A** is the more stable carbocation. The tertiary carbocation **A** has three +I groups that delocalise the charge, whereas this primary carbocation **B** has **no** +I groups which can delocalise the charge.

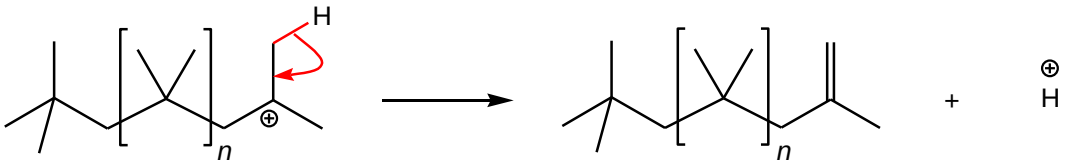
(c) Use a curly arrow to show the mechanism of step 3.

Strategy

This step involves deprotonation. The byproduct of this reaction is H^+ which comes from the heterolytic cleavage of the C-H bond. Draw a curly arrow from the centre of this C-H bond, and as the other product is an alkene, make sure the double headed arrow ends in the middle of where the alkene is formed.

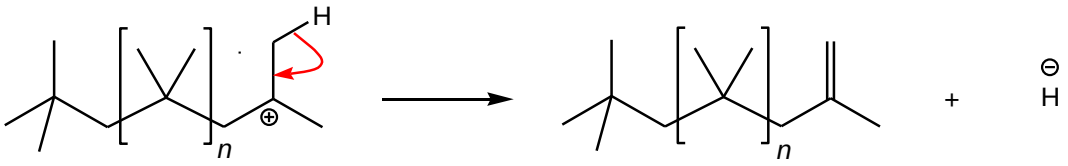
Solution

the "curly arrow" starts from the centre of the C-H bond



the "curly arrow" ends at the centre of the C-C bond

Answer



Answers to end of chapter questions (on p. 914 in *Chemistry*^{3})

1. Use the symbols +I, –I, +M, –M to identify the inductive and mesomeric effects of the following groups: (a) –Et; (b) –CHO; (c) $–NO_2$; (d) $–NH_2$; (e) $–OCH_3$; (f) $–CO_2CH_3$.

Strategy

Draw out each substituent, determine the hybridisation of its principal atom and include any non-bonded pairs of electrons. Inductive (I) and mesomeric (M) effects involve sigma and pi-frameworks respectively; a +VE sign means the substituent is electron-donating, and a –VE sign means its electron-withdrawing. Interestingly, there is no mesomeric effect for a principal atom which is sp^3-hybridised. If this principal atom is sp^2-hybridised, and contains a non-bonded pair of electrons then it has a +M effect, and if it does not, it has a –M effect. If the principal atom has an electronegative atom attached to it, it will have a –I effect, or hydrogen atoms, it will have a +I effect.

Solution

(a) -Et group; its principal atom is a sp^3-hybridised carbon atom; therefore, it has no mesomeric effect. This group has a +I effect as it can donate electron-density through hyperconjugation.

(b) –CHO group; its principal atom is a sp^2-hybridised carbon atom. As there is no non-bonded pair of electrons on this atom, it will have a –M effect. It also has a –I effect due to the electronegative β-oxygen atom.

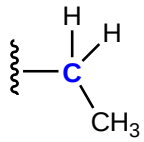
(c) $–NO_2$ group; its principal atom is a sp^2-hybridised nitrogen atom. As there is no non-bonded pair of electrons on this atom, it will have a –M effect. It also has a –I effect due to this electronegative nitrogen atom.

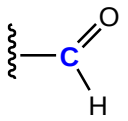
(d) $–NH_2$ group; its principal atom is a sp^2-hybridised nitrogen atom. As there is a non-bonded pair of electrons on this atom, it will have a +M effect. It also has a –I effect due to this electronegative nitrogen atom.

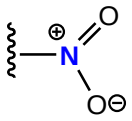
(e) –OMe group; its principal atom is a sp^2-hybridised oxygen atom. As there is (at least) one non-bonded pair of electrons on this atom, it will have a +M effect. It also has a –I effect due to this electronegative oxygen atom.

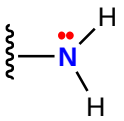
(f) $–CO_2Me$ group; its principal atom is a sp^2-hybridised carbon atom. As there is no non-bonded pair of electrons on this atom, it will have a –M effect. It also has a –I effect due to the two electronegative β-oxygen atoms.

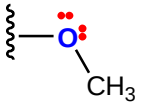
principal atoms are in blue; non-bonded pairs of electrons in red

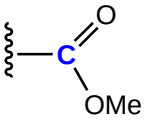
(a)  *sp*^{3}

(b)  *sp*^{2}

(c)  *sp*^{2}

(d)  *sp*^{2}

(e)  *sp*^{2}

(f)  *sp*^{2}

Answer

(a)	+I	(b)	–I, –M	(c)	–I, –M
(d)	–I, +M	(e)	–I, +M	(f)	–I, –M

2. Suggest a reason why the methyl cation and primary carbocations without resonance should never be proposed in a reaction mechanism unless no other pathway is possible

Strategy

Carbocations are high energy intermediates; they tend to lose a proton to form stable alkenes. They are generally stabilised through hyperconjugation (using the sigma electrons of their adjacent β-C-H bonds) which helps stabilise the empty 2*p*-atomic orbital on their α-C-atom. This has been illustrated on p. 866 in *Chemistry*^{3}.

Solution

With all things being equal, the relative stability of substituted carbocations is:
tertiary carbocations (R_3C^+) > secondary carbocations (R_2CH^+) > primary carbocations (RCH_2^+) > methyl carbocations (CH_3^+)

A methyl carbocation is particularly unstable due to lack of hyperconjugation (there are no β-C-H bonds). Primary carbocations are slightly more stable due to potential hyperconjugation. If there is a possibility of resonance stabilisation, the stability of this primary carbocation will be greatly increased.

Answer

Primary carbocations without resonance, and especially the methyl carbocation, are extremely unstable cations. It is unlikely that these carbocations will exist as intermediates in reactions if other pathways are possible.

3. Explain why the allyl radical ($H_2C{=}CH{-}CH_2{\cdot}$) is more stable than a *tert*-butyl radical ($Me_3C{\cdot}$).

Strategy

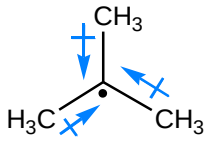
Draw out the structures of the allyl radical ($H_2C{=}CH{-}CH_2{\cdot}$) and the tertiary radical ($Me_3C{\cdot}$). Determine if there are inductive effects; if so does this involve hyperconjugation? Are there any mesomeric (resonance) effects?

Solution

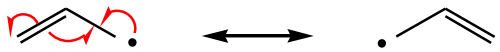
At a glance, the tertiary radical may appear to be more stable than a primary radical because of a greater opportunity for hyperconjugation. However, this primary radical is in fact an allyl radical, which is resonance stabilised by conjugating with its neighbouring alkene.

Answer

Although the *tert*-butyl radical is stabilised by hyperconjugation and the +I effects of the methyl groups, the allyl radical is more stable than the *tert*-butyl radical because it is stabilised by resonance.

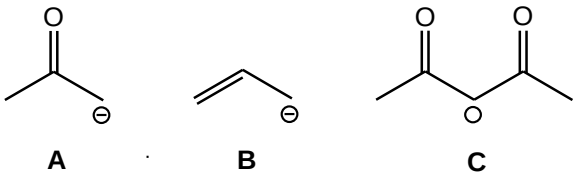


tert-butyl radical



allyl radical

4. Rank the following carbanions (**A**–**C**) in order of increasing stability. Explain your reasoning.

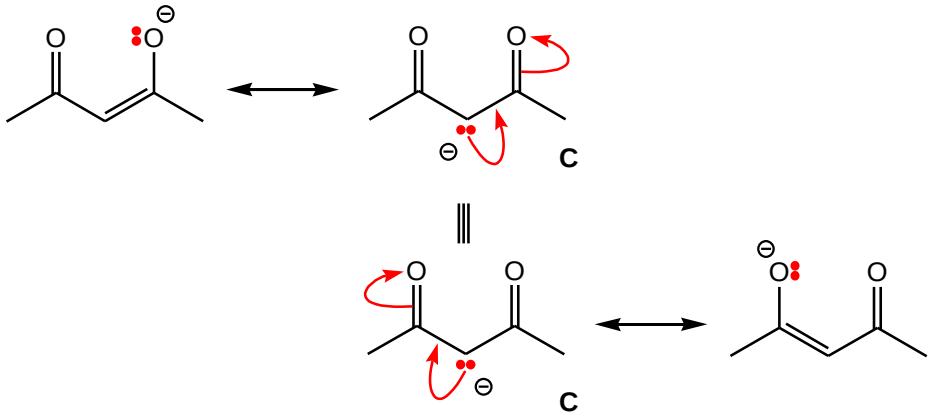


Strategy

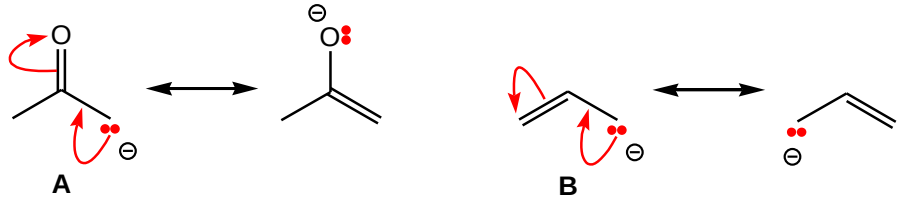
In order to judge the relative stability of these carbanions, **A**-**C**, you will need to draw out and examine the quantity and quality of all potential resonance structures. [All these carbanions have resonance stabilisation.]

Solution

Carbanion, **C**, has two additional resonance structures where the negative charge can be positioned from its carbon atom onto its more electronegative oxygen atom; both of these **conjugated** resonance structures are identical.



Carbanion, **A**, can also conjugate its negative charge from its carbon atom onto its oxygen atom; however there is only one additional resonance structure. This carbanion is **less stable** than carbanion, **C**.

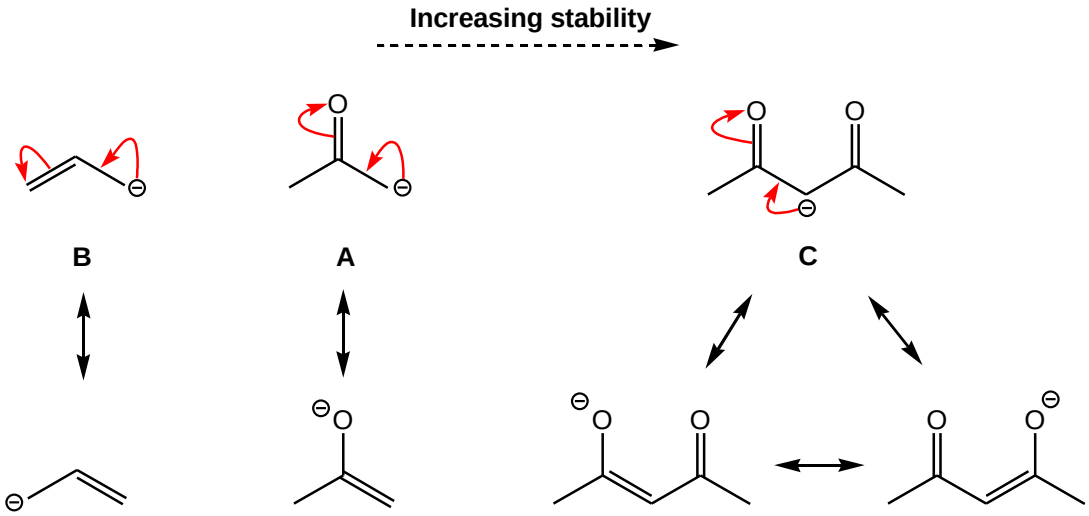


Carbanion, **B**, can conjugate its negative charge from its carbon atom onto the carbon atom of the neighbouring alkene. These two identical resonance structures are **less stable** than those of carbanion, **A**.

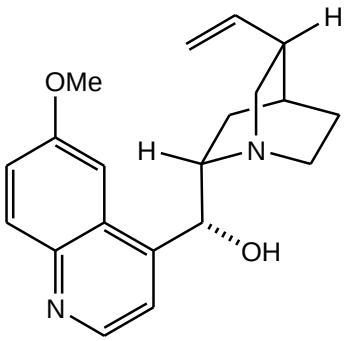
Overall, the stability of these carbocations are **C** > **A** > **B**.

Answer

Order: **B** (least stable) < **A** < **C** (most stable). Carbanion **C** is the most stable anion because it has three resonance forms two of which have the negative charge on an electronegative oxygen atom – a negative charge on an oxygen atom is more stable than a negative charge on a carbon atom. Carbanions **A** and **B** both have two resonance forms but carbanion **A** is the more stable because one of the resonance forms has a negative charge on its oxygen atom.



5. The following questions relate to quinine, a naturally occurring antimalarial agent.



quinine

(a) (i) Identify, giving your reasons, the most acidic hydrogen atom in quinine.

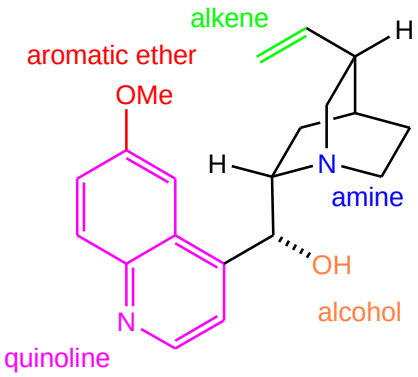
(ii) Draw the product from the reaction of quinine with sodium hydride (Na^+H^-) and give a mechanism (using curly arrows) to show its formation.

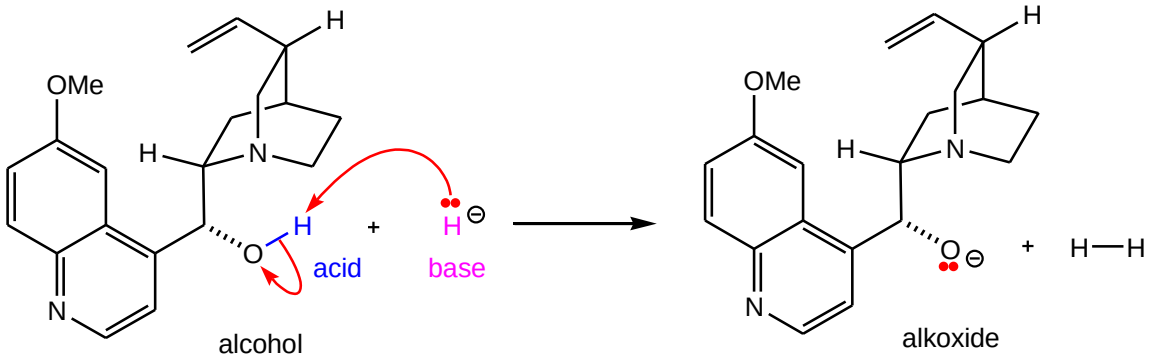
Strategy

Name all the functional groups present in this molecule (this might give you a clue to which proton is the most acidic). Using hydride, H^-, as the Brønsted base, remove the most acidic proton from this molecule. For this mechanism, you will need two "curly arrows"; one from the hydride to the proton of your chosen Brønsted acid (→), and one from the centre of this C-H bond to the principal atom of this acid (→).

Solution

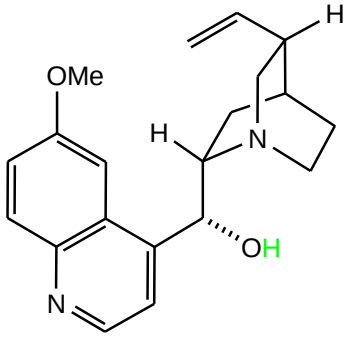
There are five functional groups (alcohol, alkene, amine, aromatic ether and quinoline). The alcohol group contains the most acidic proton (pK_a = 16) as its conjugate base, alkoxide, is stabilised by its highly electronegative oxygen atom. The curly arrow mechanism for this process is shown below. [Note: hydride, H^-, contains a pair of non-bonded electrons.]





Answer

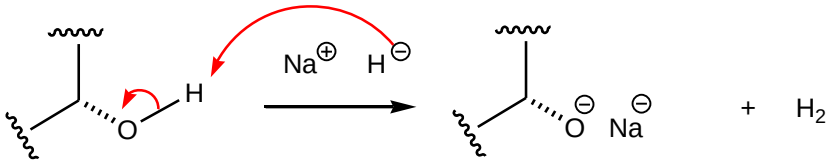
(i)



most acidic H

the electronegative oxygen atom stabilises the negative charge of the conjugate base

(ii)



Partial structure of quinine

(b) (i) Identify, giving your reasons, the most basic functional group in quinine.

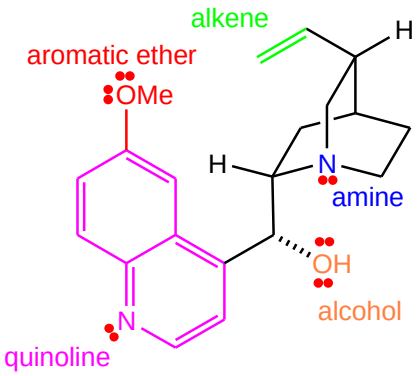
(ii) Draw the product from the reaction of quinine with hydrogen chloride (H–Cl) and give a mechanism (using curly arrows) to show its formation.

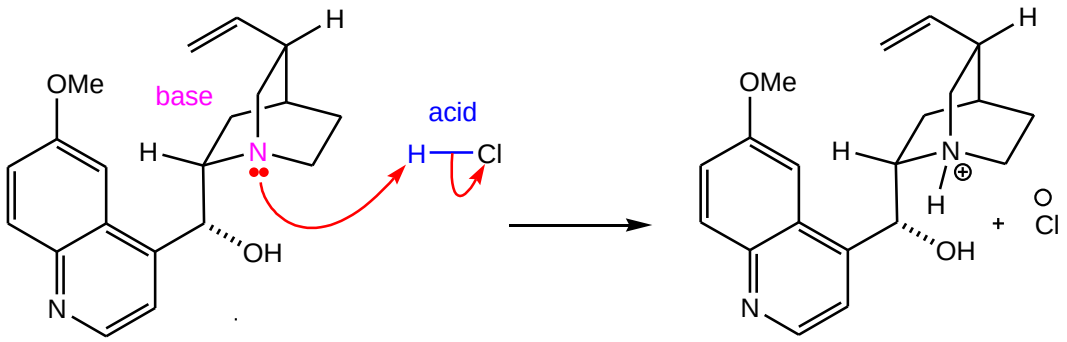
Strategy

Name all the functional groups present in this molecule and include all non-bonded pairs of electrons (this might give you a clue to which principal atom is the most basic). Using hydrogen chloride, H-Cl, as the Brønsted acid, remove this proton using the principal atom of your chosen Brønsted base. For this mechanism, you will need two "curly arrows"; one from the principal atom of your chosen Brønsted base to the proton of H-Cl (→), and one from the centre of this H-Cl bond to the principal atom of this acid, Cl (→).

Solution

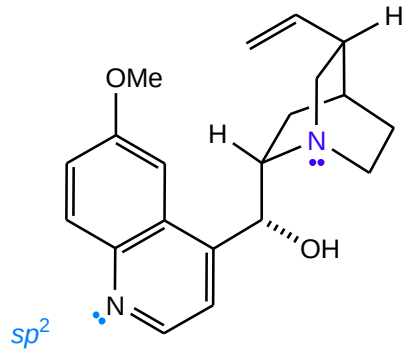
There are five functional groups (alcohol, alkene, amine, aromatic ether and quinoline). The tertiary amine group is the most basic group as it contains the more basic nitrogen atom; sp^3-hybridised amines are more basic than sp^2-hybridised quinolines as their non-bonded pair of electrons is higher in energy. The alcohol and ether are less basic as their principal atom is a highly electronegative oxygen atom. The curly arrow mechanism for this process is shown below.





Answer

(i)

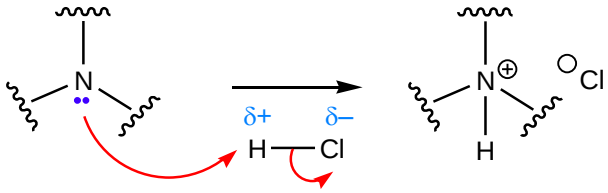


most basic site

amines are more basic than alcohols or ethers because nitrogen is less electronegative than oxygen

the lone pair onthis nitrogen atom is in an sp^3 orbital and this is more basic than a lone pair in an sp^2 orbital

(ii)



Partial structure of quinine

(c) (i) Identify, giving your reasons, the most nucleophilic site in quinine.

(ii) Draw the product from the reaction of quinine with CH_3Br and give a mechanism (using curly arrows) to show its formation.

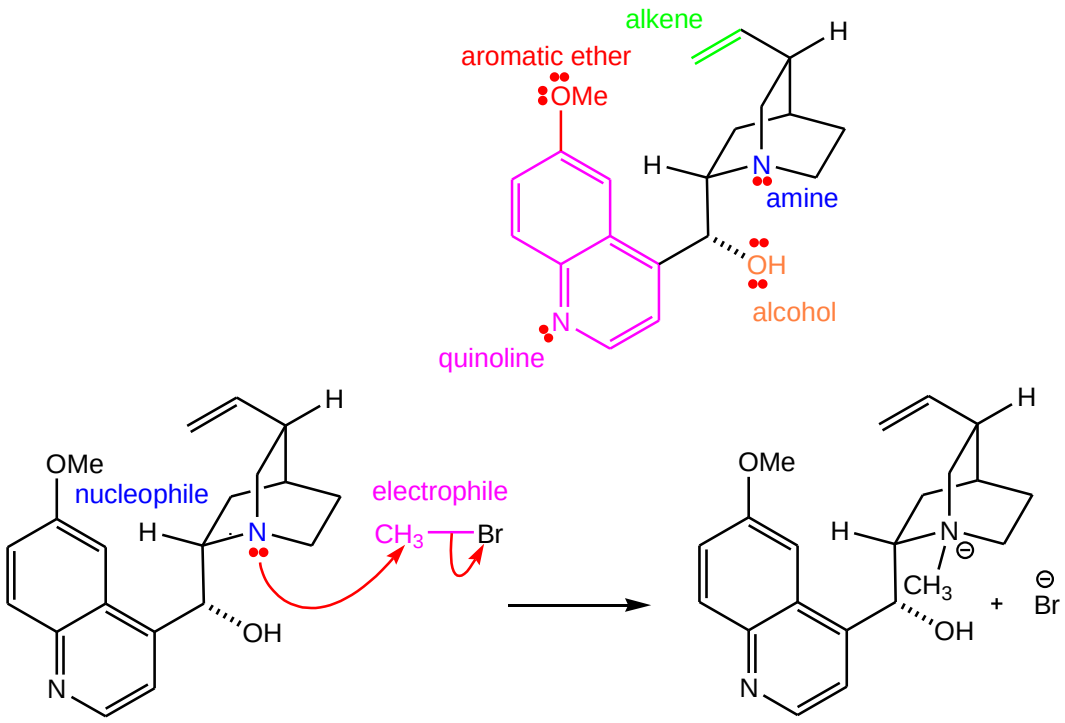
Strategy

Name all the functional groups present in this molecule and include all non-bonded pairs of electrons (this might give you a clue to which principal atom is the most nucleophilic). Using methyl bromide, CH_3-Br, as the electrophile; transfer this methyl (CH_3) group using the principal atom of your chosen nucleophile. For this mechanism, you will need

two "curly arrows"; one from the principal atom of your chosen nucleophile to the methyl group of CH_3-Br (→), and one from the centre of this CH_3-Br bond to the principal atom of this electrophile, bromide (→).

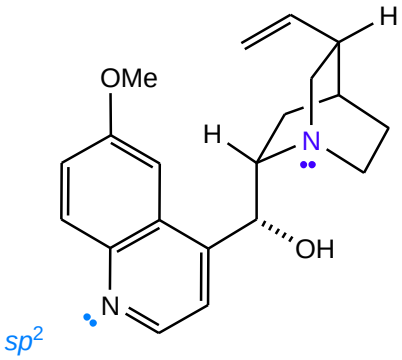
Solution

There are five functional groups (alcohol, alkene, amine, aromatic ether and quinoline). The tertiary amine group is the most nucleophilic group as it contains the more nucleophilic nitrogen atom; sp^3-hybridised amines are more nucleophilic than sp^2-hybridised quinolines as their non-bonded pair of electrons is higher in energy. The alcohol and ether are less nucleophilic as their principal atom is a highly electronegative oxygen atom. The curly arrow mechanism for this process is shown below.



Answer

(i)

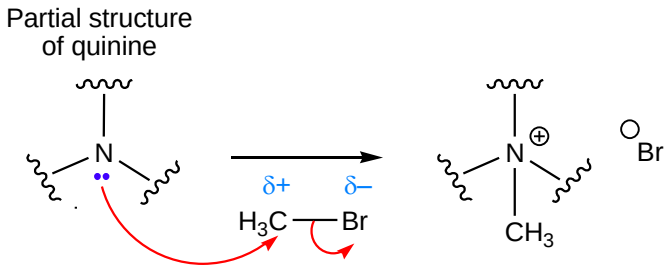


most nucleophilic site

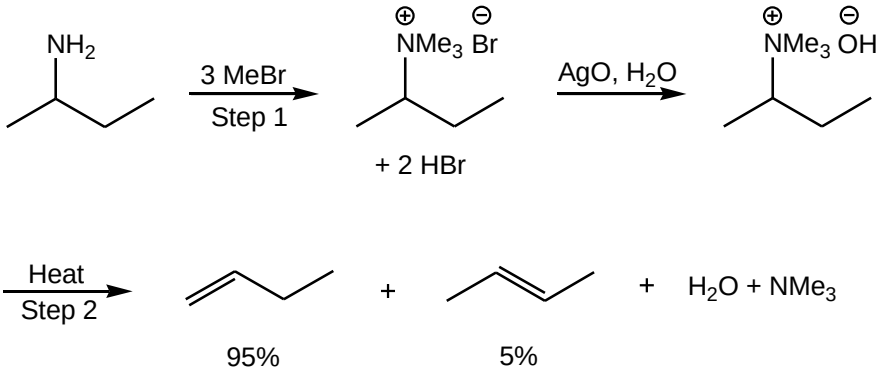
amines are more nucleophilic than alcohols or ethers because nitrogen is less electronegative than oxygen.

the lone pair on this nitrogen atom is in an sp^3 orbital and this is more nucleophilic than a lone pair in an sp^2 orbital

(ii)



6. The following questions relate to the sequence of reactions shown below.



(a) What type of polar reaction is taking place in step 1?

Strategy

Examine the reagents, and work out if they are electrophile/nucleophile or acid/base combinations. Work out if this reaction is an addition, substitution or elimination.

Solution

This reaction involves substituting three N-H bonds for three N-Me groups. [Alternatively, this reaction is a substitution as it is neither an addition nor elimination.] As the principal reagent is a nucleophile; this reaction therefore involves **nucleophilic substitution**.

Answer

Three nucleophilic substitution reactions take place in step 1.

(b) What type of polar reaction is taking place in step 2?

Strategy

Examine the reagents, and work out if they are electrophile/nucleophile or acid/base combinations. Work out if this reaction is an addition, substitution or elimination.

Solution

This reaction involves elimination of H_2O and NMe_3 from the parent ammonium hydroxide, and involves an acid/base combination. As the principal reagent is a base; this reaction therefore involves base-mediated elimination.

Answer

An elimination reaction (called a Hofmann elimination reaction, see box 20.5 on p. 941 in *Chemistry*^{3}).

(c) Explain why the reaction in step 2 is a regioselective reaction.

Strategy

For a step to be regioselective, it must involve the formation of two or more regioisomers and it must be selective; *i.e.*, **regioselective**. If there is a **choice** within its mechanism, then it will always be **selective**.

Solution

There are two regioselective alkenes formed. This process must be regioselective.

Answer

The elimination is highly regioselective because it leads to the selective formation of one structural isomer over another – but-1-ene (a terminal alkene) is formed in much higher yield than but-2-ene (an internal alkene).

(d) Explain why the reaction in step 2 is a stereoselective reaction.

Strategy

For a step to be stereoselective, it must involve the formation of stereoisomers (stereo-) and it must be selective; *i.e.*, **stereoselective**. If there is a **choice** within its mechanism, then it will always be **selective**.

Solution

This elimination step has the potential to form *cis*- and *trans*-but-2-enes. It selectively forms the major *trans*-but-2-ene [(*Z*)-alkene]; the minor *cis*- but-2-ene [(*E*)-alkene] is not drawn. This reaction is a stereoselective process.

Answer

The elimination is stereoselective because it leads to the selective formation of the (*E*)-isomer, rather than the (*Z*)-isomer, of but-2-ene.

Solutions provided by J. Eames (j.eames@hull.ac.uk)