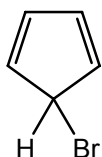

Benzene and other aromatic compounds: electrophilic substitution reactions

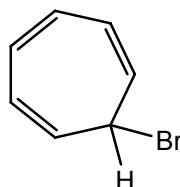
Answers to worked examples

WE 22.1 Aromatic and anti-aromatic compounds (on p. 1005 in *Chemistry*³)

5-Bromocyclopenta-1,3-diene is insoluble in water, whereas adding water to 7-bromocyclohepta-1,3,5-triene rapidly produces a water-soluble salt. Suggest an explanation for the different behaviour.



5-bromocyclopenta-1,3-diene



7-bromocyclohepta-1,3,5-triene

Strategy

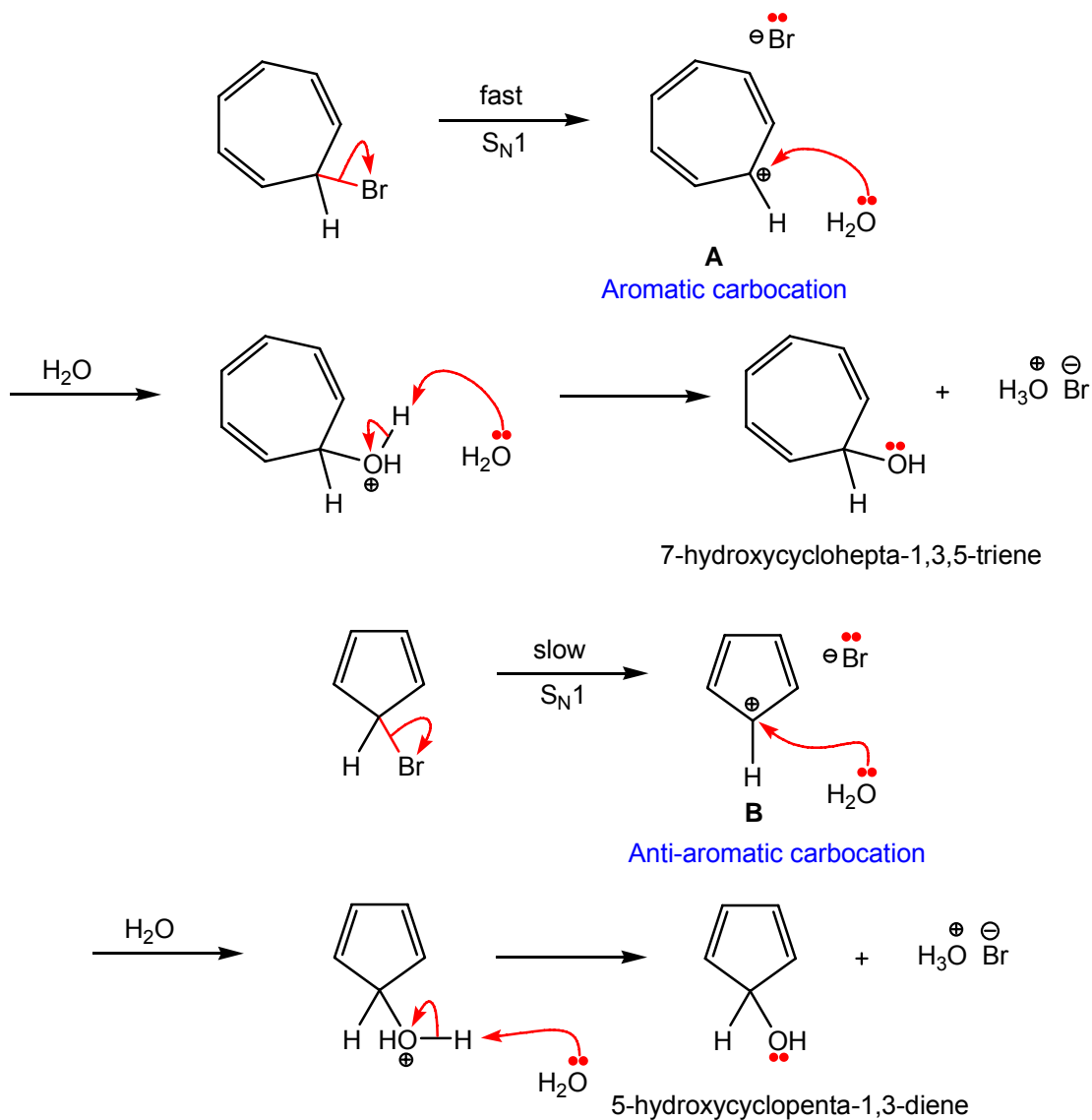
Both conjugated bromides are insoluble in water. 7-Bromocyclohepta-1,3,5-triene will dissolve in water by reacting with it. In essence, the rate of this bromide displacement must be faster for 7-bromocyclohepta-1,3,5-triene than 5-bromocyclopenta-1,3-diene as this does not dissolve in water.

Solution

7-Bromocyclohepta-1,3,5-triene readily reacts with water, by a S_N1 mechanism, to give the water-soluble 7-hydroxycyclohepta-1,3,5-triene. This reaction proceeds by formation of a stabilised **aromatic carbocation A**. By comparison, 5-bromocyclopenta-1,3-diene reacts much slower with water, by a S_N1 mechanism, to give its water-soluble product,

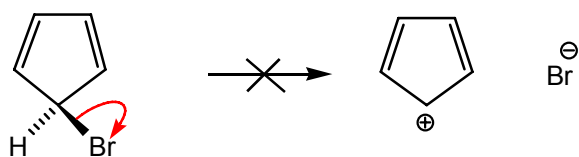
5-hydroxycyclopenta-1,3-diene, as its intermediate carbocation **B** is significantly less stable than **A** due to its **anti-aromatic** character.

[To recap: for a molecule to be (a) aromatic it must be cyclic, planar, have uninterrupted (continuous) conjugation, and $(4n + 2)$ -pi-electrons; and (b) anti-aromatic it must be cyclic, planar, have uninterrupted (continuous) conjugation, and $(4n)$ -pi-electrons.]

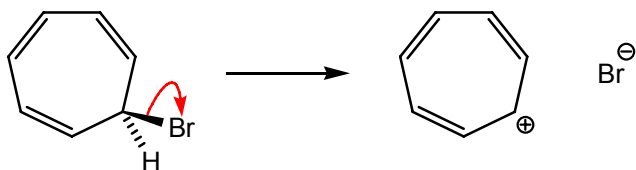


Answer

5-Bromocyclopenta-1,3-diene and 7-bromocyclohepta-1,3,5-triene react differently in water because their intermediate carbocations (formed by heterolytic cleavage of their corresponding C–Br bond) have different stabilities.



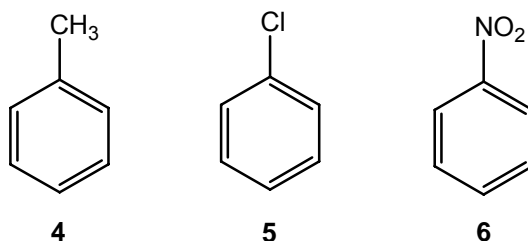
The cyclopentadienyl cation has four π -electrons and is **antiaromatic**



The cycloheptatrienyl cation has six π -electrons and is **aromatic**

WE 22.3 The effect of existing substituents on electrophilic substitutions (on p. 1028 in *Chemistry*³)

The following queries are based on the bromination of compounds **4–6** using Br_2 and FeBr_3 to give mono-brominated products.



(a) Do compounds **4–6** react faster or slower than benzene with Br_2 and FeBr_3 ?

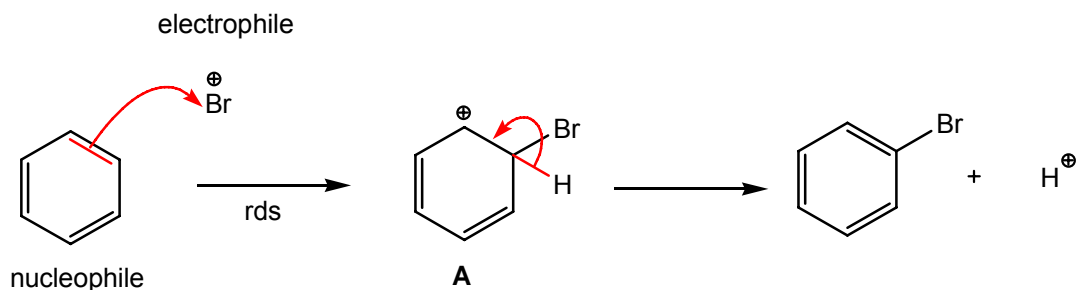
Strategy

The rate of these reactions will depend on the relative reactivity of these mono-substituted benzenes. In order to determine this, you must decide which components are the electrophile and nucleophile in this reaction, and what might be the rate-determining step in these bromination reactions.

Solution

This reaction is an electrophilic bromination; the Br^+ ion (or the $\text{Br}_2\text{-FeBr}_3$ complex) is the electrophile and benzene ring is the nucleophile. The rate-determining step is electrophilic

addition of this bromonium ion, Br^+ , to the benzene ring, to form an intermediate conjugated carbocation, **A**. Deprotonating this intermediate carbocation, **A**, reforms the aromatic ring to give the required product, bromobenzene.



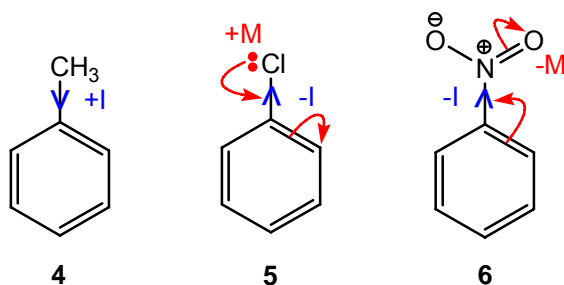
As the electrophile, Br^+ , is common in all of these reactions, altering the nucleophilicity of the chosen nucleophile will alter the rate of electrophilic addition; the more nucleophilic the substituted benzene the faster the addition process.

Toluene, **4**, is more electron rich and a better nucleophile than benzene due to the electron-donating effect (+I effect) of its methyl group.

Chlorobenzene, **5**, is less electron rich and a poorer nucleophile than benzene due to the overall electron-withdrawing effect (-I effect > +M effect) of its chlorine substituent.

Nitrobenzene, **6**, is less electron rich and a poorer nucleophile than benzene due to the electron-withdrawing effect (-I effect and -M effect) of its nitro group.

Comparing these reactions, the relative rate of bromination is (fastest) toluene > benzene > chlorobenzene > nitrobenzene (slowest).



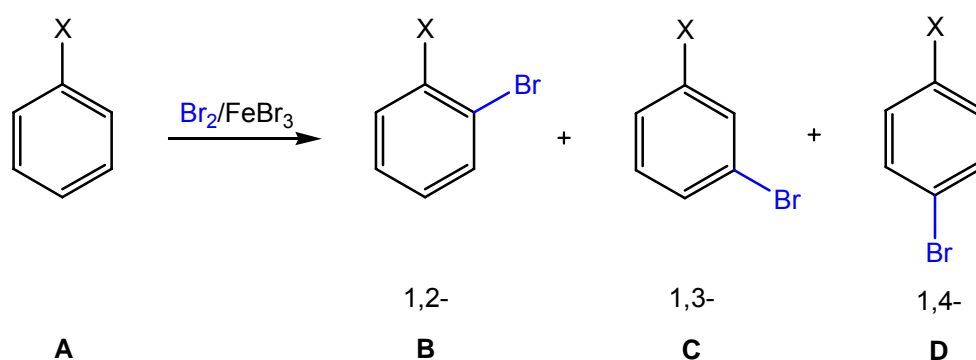
Answer

Compound **4** reacts faster than benzene (CH_3 is a 2,4-directing activator). Compound **5** reacts slower than benzene (Cl is a 2,4-directing deactivator). Compound **6** reacts slower than benzene (NO_2 is a 3-directing deactivator).

- (b) Give the structure(s) of the major product(s) from reaction of **4–6** with Br₂ and FeBr₃

Strategy

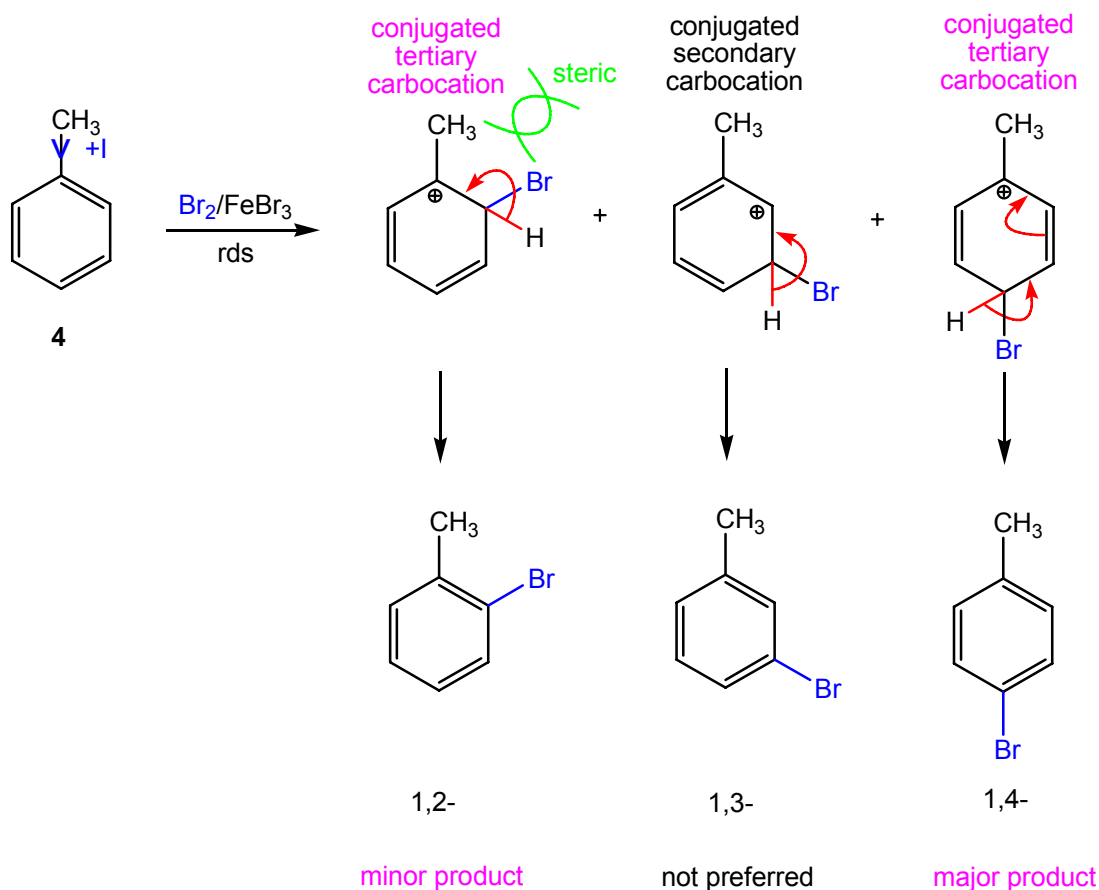
Bromination of benzene leads to a single product because all the carbon atoms are identical. For mono-substituted benzenes, such as **A**, up to three products **B**, **C** and **D** are formed. Regioselective bromination will depend on which positions in this molecule are more nucleophilic, and thus better equipped at stabilising the intermediate conjugated carbocations.



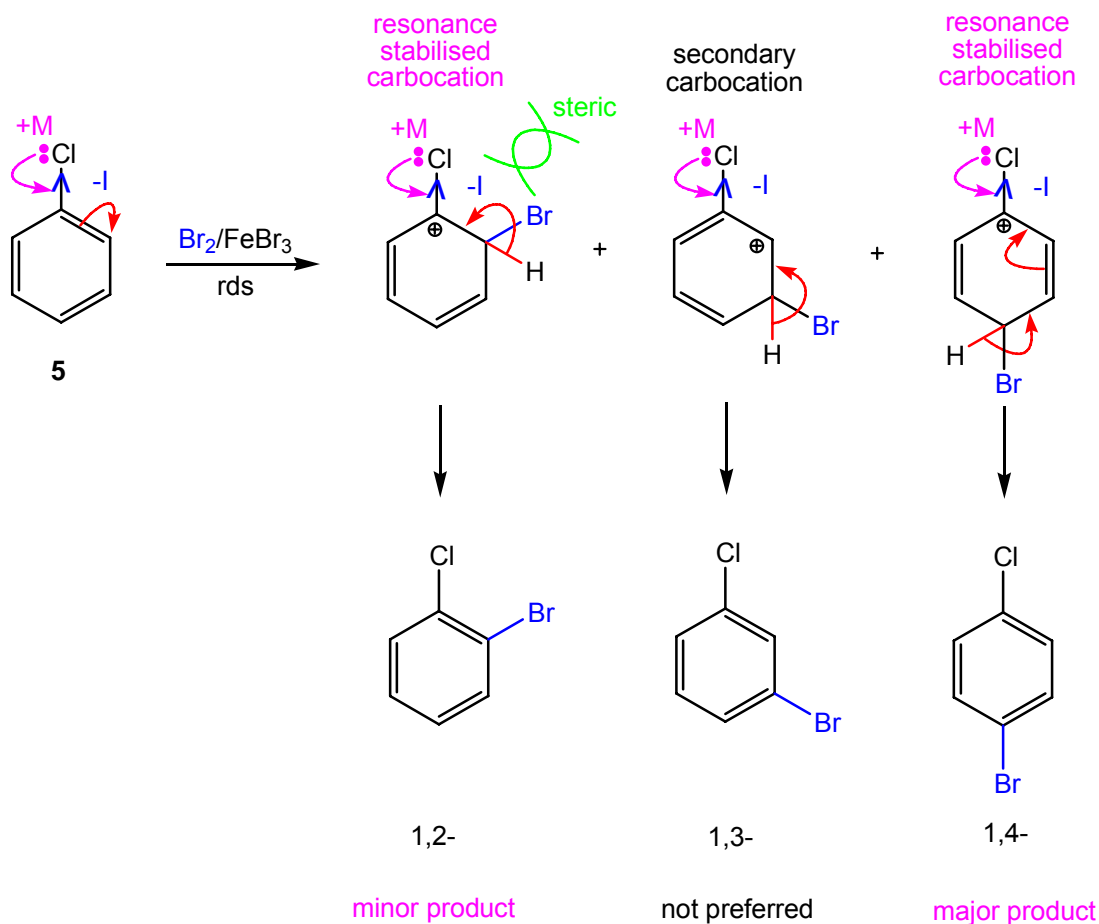
Draw out all potential products from the bromination of toluene (**4**), chlorobenzene (**5**) and nitrobenzene (**6**), and work out which carbon atoms in these molecules are the most nucleophilic.

Solution

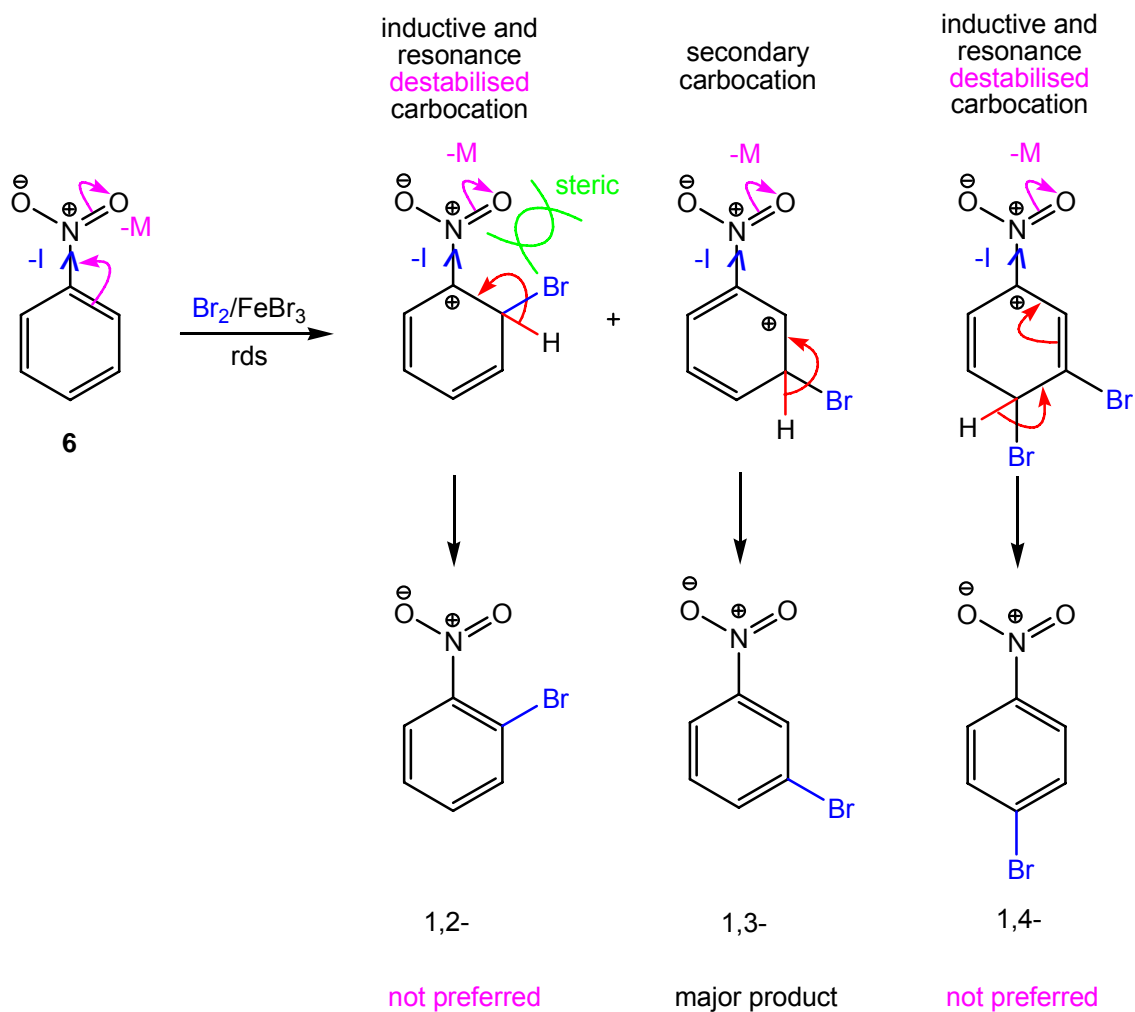
For toluene, **4**, only two of the three potential products are formed. The major and minor products are 4-bromotoluene and 2-bromotoluene, respectively. The remaining product, 3-bromotoluene is not formed. Bromination preferentially occurs on carbons-2 and -4 to give 2-bromotoluene and 4-bromotoluene as their intermediate tertiary carbocations are stabilised by the electron-donating methyl group (+I effect). However, bromination at carbon-2 is slightly less preferred due to steric congestion between the Br and Me groups. 3-Bromotoluene is not formed as its intermediate secondary carbocation is less stable.



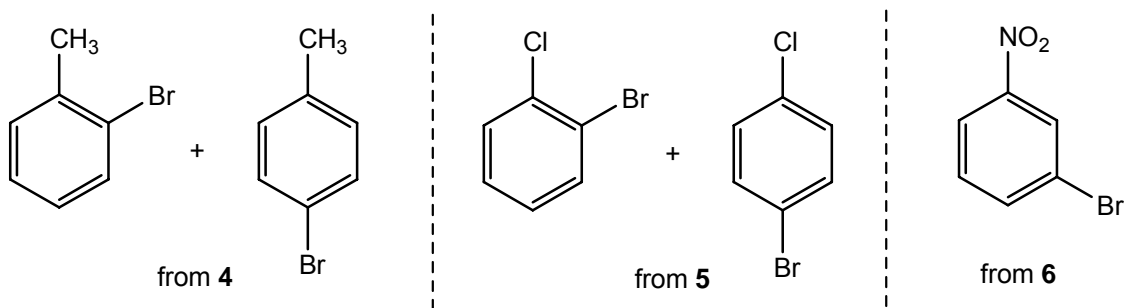
For chlorobenzene, **5**, only two of the three potential products are formed. The major and minor products are 1-bromo-4-chlorobenzene and 1-bromo-2-chlorobenzene, respectively. The remaining product, 1-bromo-3-chlorobenzene is not formed. Bromination preferentially occurs on carbons-2 and -4 to give 1-bromo-4-chlorobenzene and 1-bromo-2-chlorobenzene, respectively, as their intermediate carbocations are resonance stabilised by the electron-donating chlorine group (+M effect). However, bromination at carbon-2 is slightly less preferred due to steric congestion between the Cl and Me groups. 1-Bromo-3-chlorobenzene is not formed as its intermediate secondary carbocation is less stable as it is not resonance stabilised by its chlorine substituent.



For nitrobenzene, **6**, only one of the three potential products is formed. The major product is 1-bromo-3-nitrobenzene. The remaining potential products, 1-bromo-2-nitrobenzene and 1-bromo-4-nitrobenzene are not formed. Bromination preferentially occurs on carbon-3 to give 1-bromo-3-nitrobenzene as its intermediate carbocation is **not destabilised** by the electron-withdrawing nitro group ($-\text{M}$ and $-\text{I}$ effects).



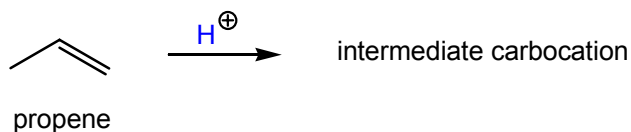
Answer



Answers to boxes

Box 22.2 Making phenol from benzene (on p. 1001 in *Chemistry*³)

- (a) In step 1, an intermediate carbocation is formed by regioselective addition of H^+ to propene. Draw the structure of the carbocation and explain why the addition is regioselective (*Hint*: see section 21.3 on p. 966 in *Chemistry*³.)



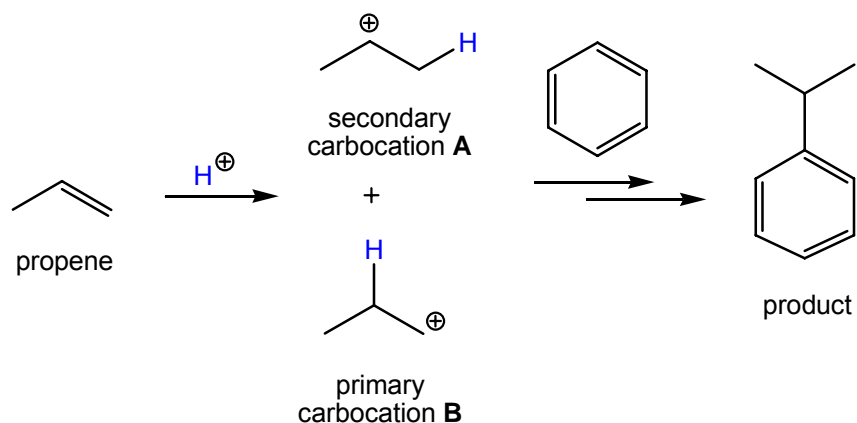
Strategy

Propene must be the base, as H^+ is the acid. As this alkene is unsymmetrical, protonation will give TWO carbocations. Work out the structure of these carbocations, and deduce which one is more stable. Using this information, explain the term *regioselective*.

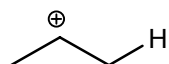
Solution

Protonation of propene leads to TWO carbocations **A** and **B**. The secondary carbocation, **A**, is more stable than primary carbocation, **B**, due to increased hyperconjugation (+I effect from the Me group). Electrophilic addition of benzene with the more stable carbocation **A** gives the required product. This protonation is regioselective, as both carbon atoms of the double ($\text{C}=\text{C}$) bond of propene are different, and therefore protonation will occur selectively on either carbon atom of this alkene to give potentially two carbocations **A** and **B**.

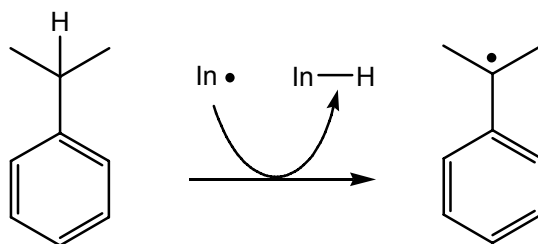
For a reaction to be regioselective, it must involve the formation of regioisomers (carbocations) and it must be selective; *i.e.*, **regioselective**. If there is a **choice** within its mechanism, then it will always be **selective**.

Answer

H^+ adds to the terminal carbon atom of the $\text{C}=\text{C}$ bond to form the more stable carbocation.



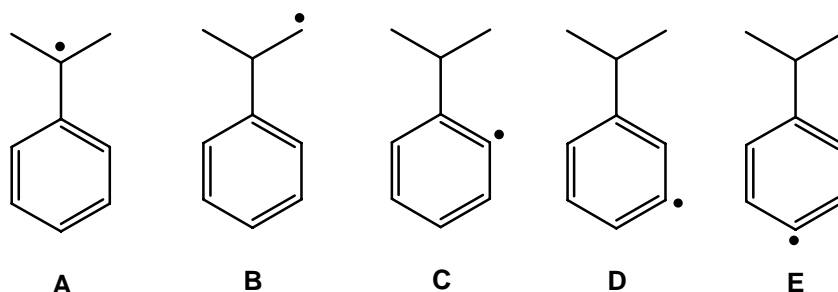
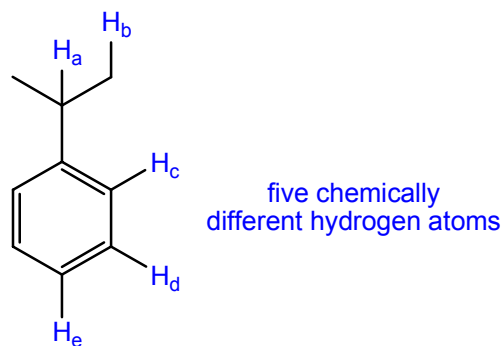
- (b) Explain why the radical initiator (In^\bullet) selectively abstracts a hydrogen atom from the tertiary carbon atom of 1-methylethylbenzene in step 2.

Strategy

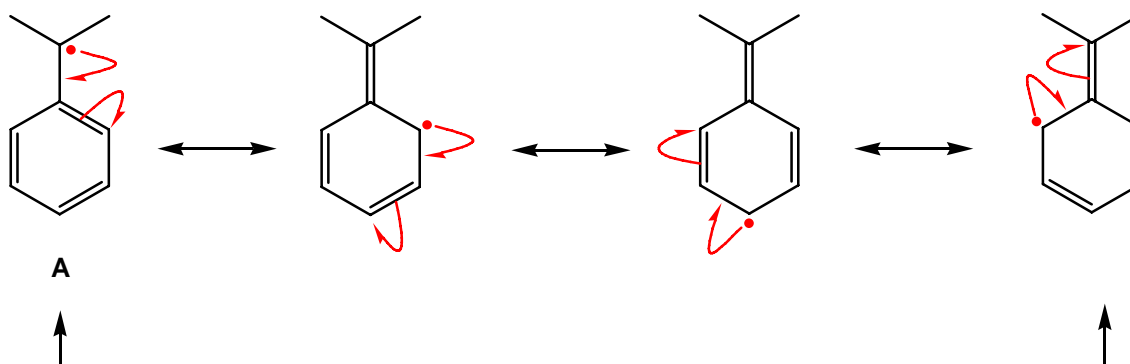
Radical reactions are generally under thermodynamic (stability) control, and as such, prefer the formation of stable radicals. Draw out all potential radicals, derived from hydrogen abstraction of isopropylbenzene, and deduce which one is the most stable.

Solution

There are FIVE different hydrogen atoms, H_a - H_e , in isopropylbenzene. Alkyl groups contain weaker C-H bonds (H_a and H_b) than the alkenyl groups (H_c , H_d and H_e). The bond strengths for alkyl C-Hs are primary (strongest) > secondary > tertiary (weakest); therefore removal of H_a is the easiest as it has the weakest C-H bond. In addition, radical hydrogen abstraction of H_a with In^\bullet leads to the most stable (tertiary) radical, which is additionally stabilised through conjugation with its neighbouring phenyl ring.

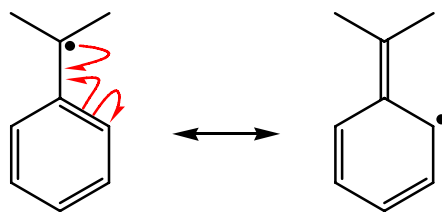


Resonance stabilised tertiary radical **A**.



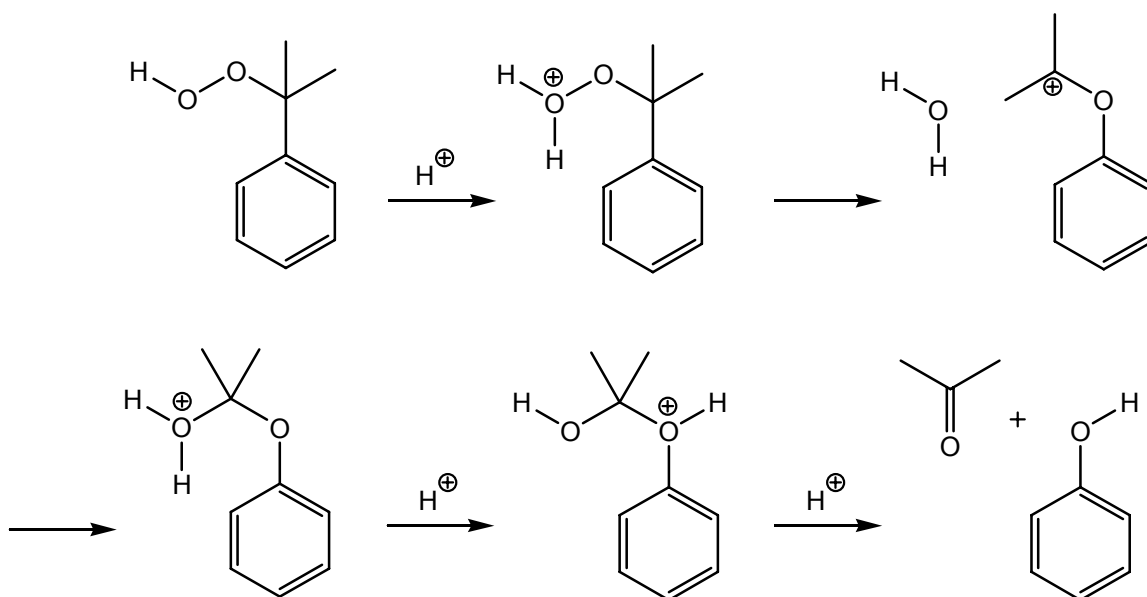
Answer

The radical initiator selectively abstracts a hydrogen atom from the tertiary carbon because the tertiary C–H bond is the weakest bond in 1-methylethylbenzene. It is the weakest C–H bond because abstraction of the hydrogen atom forms a relatively stable tertiary carbon radical, which is stabilised by resonance.



a tertiary carbon
radical stabilised
by resonance

- (c) Suggest a reaction mechanism, using curly arrows, to explain how cumene hydroperoxide is converted into phenol and propanone in step 3. (Note: this mechanism involves ionic intermediates and not radical intermediates as in step 2.)

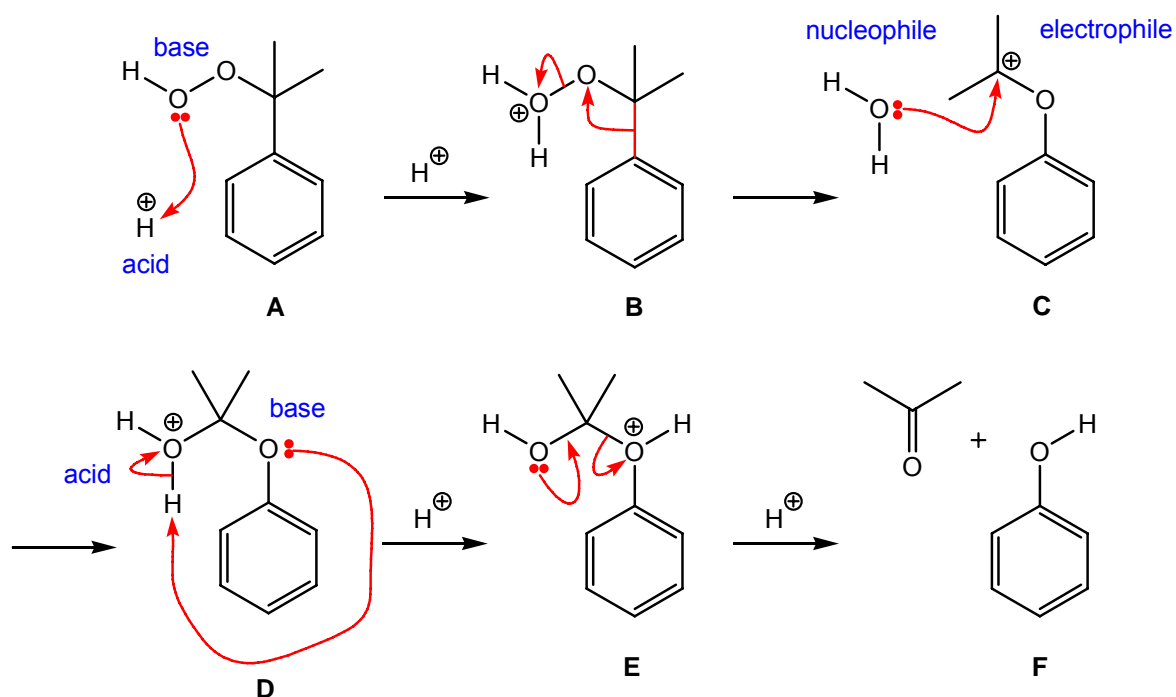


Strategy

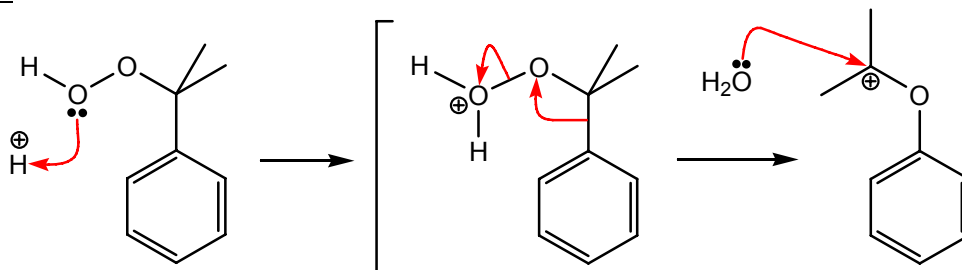
The intermediates in this mechanism are given above. You must first highlight on your scheme any non-bonded pairs of electrons. Secondly, for each step, you will need to decide whether the reaction involves an electrophile/nucleophile or acid/base combination. Acid and base processes involve proton exchange, whereas, electrophile and nucleophile processes involve bond-breaking and bond-making. Draw a curly arrow from the nucleophile or base to the electrophile or acid (\rightarrow). When intermediates are formed, use nucleophile/base and electrophile/acid combinations to give more stable intermediates and/or products.

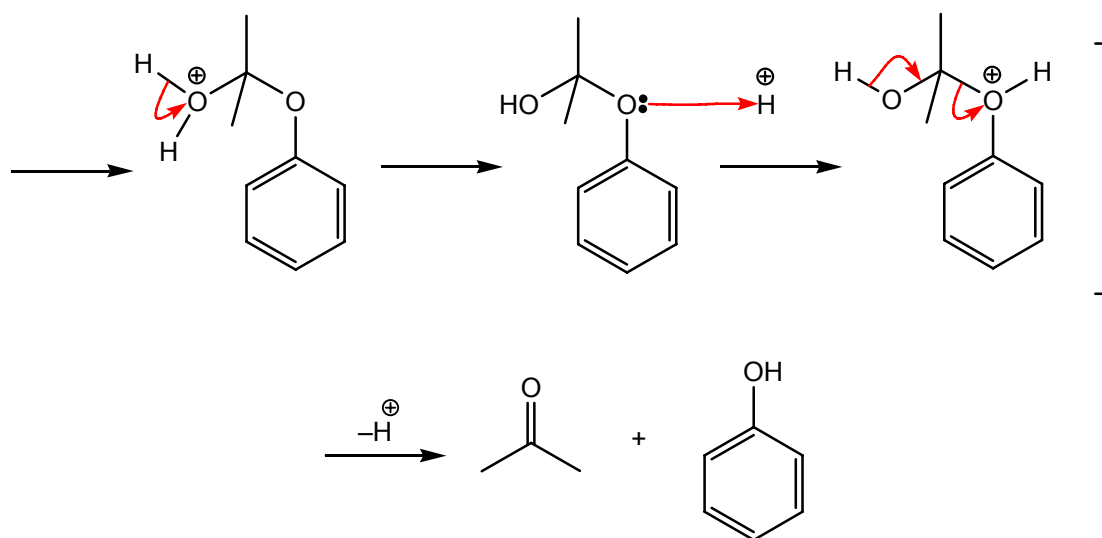
Solution

Converting the hydroperoxide **A**, which contains a very weak O-O bond into propanone (which has a strong C=O bond) and phenol **F** (which is resonance stabilised) is the driving force of this reaction. Protonation of hydroperoxide **A** with H^+ leads to the oxonium ion **B**. This oxonium ion, **B**, fragments by loss of water (H_2O) using a 1,2-phenyl shift to give the resonance-stabilised carbocation **C**. Nucleophilic addition of water (H_2O) to this carbocation **C** leads to the oxonium ion/hemiketal **D**. Internal proton exchange (in **D**), followed by loss of phenol **F** (in **E**) generates the important carbonyl (C=O) group in propanone. The mechanism for this rearrangement is shown below: the red components highlight the important movement of non-bonded and bonded electrons.

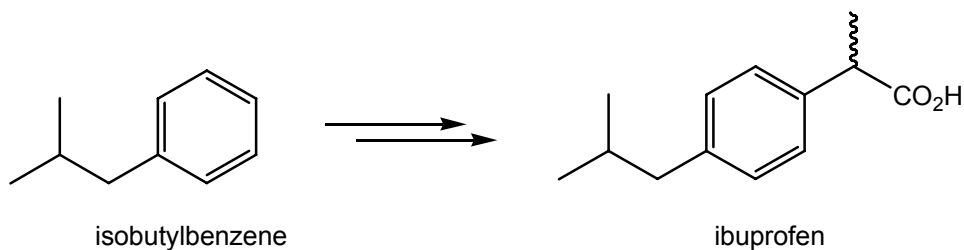


Answer

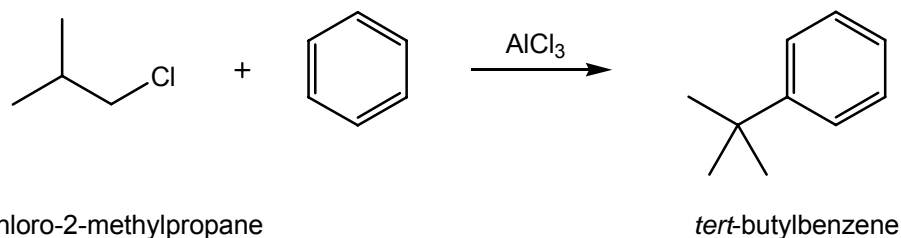


**Box 22.4 Substituted benzenes in sport (on p. 1015 in *Chemistry*³)**

Ibuprofen is an anti-inflammatory drug used by athletes to relieve minor aches and pains and to help reduce minor swelling. Ibuprofen is sold as a racemate (see box 10.7 on p. 483 in *Chemistry*³) and is prepared on an industrial scale from isobutylbenzene.



Isobutylbenzene is prepared in industry using a two-step sequence [Friedel–Crafts acylation followed by reduction of the C=O bond (see p. 1019 in *Chemistry*³)]. This is because attempts to prepare isobutylbenzene in a single step, by reacting benzene with 1-chloro-2-methylpropane and AlCl_3 , gave *tert*-butylbenzene as the major product. Suggest a reaction mechanism to explain the formation of *tert*-butylbenzene, rather than isobutylbenzene, from the reaction below.

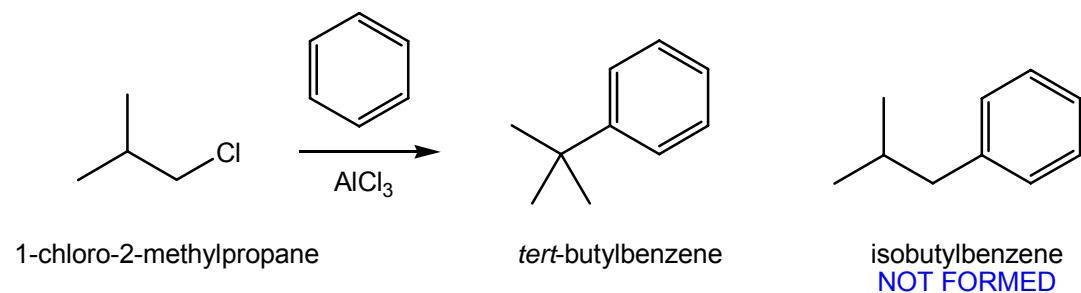


Strategy

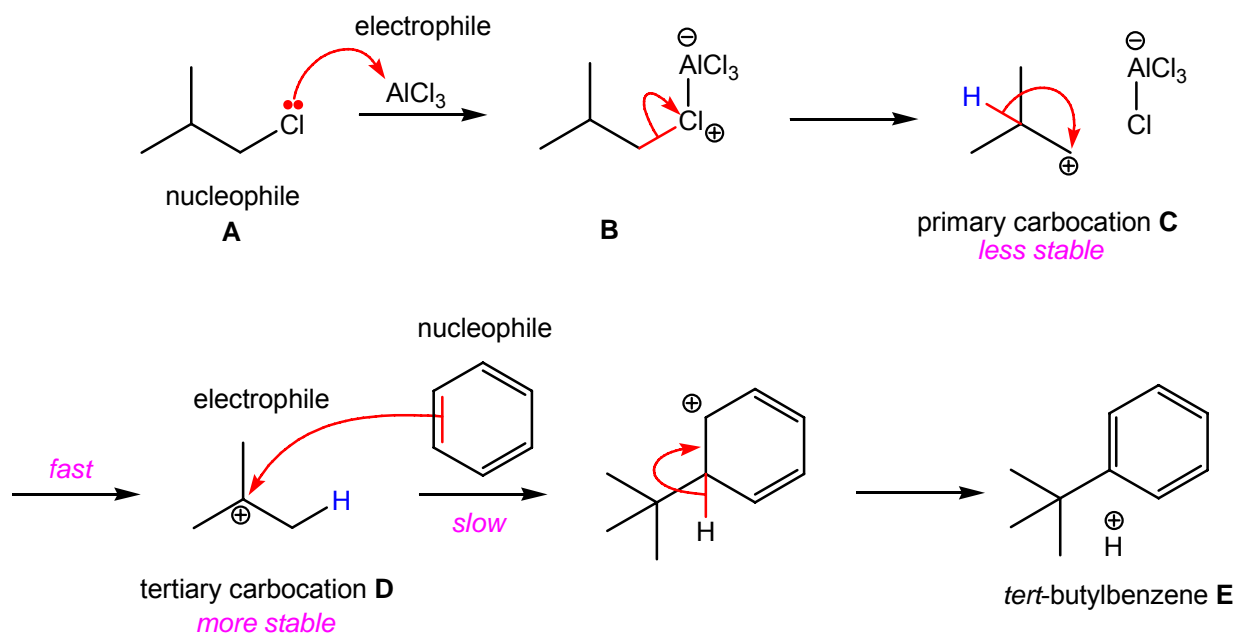
Draw out the reagents and a general scheme for this reaction. Work out which reagent is the nucleophile and electrophile. [Remember, the “curly arrow” flows from the nucleophile (\rightarrow) to the electrophile.] Nucleophiles contain non-bonded electrons (which sometimes can be depicted by negative charge) and electrophiles have low-lying empty orbitals (which often contain a leaving group). Draw the mechanism of this reaction, and suggest why *tert*-butylbenzene, rather than isobutylbenzene is formed. A related mechanism for this reaction has been discussed on pages 967 and 1017 in *Chemistry*³.

Solution

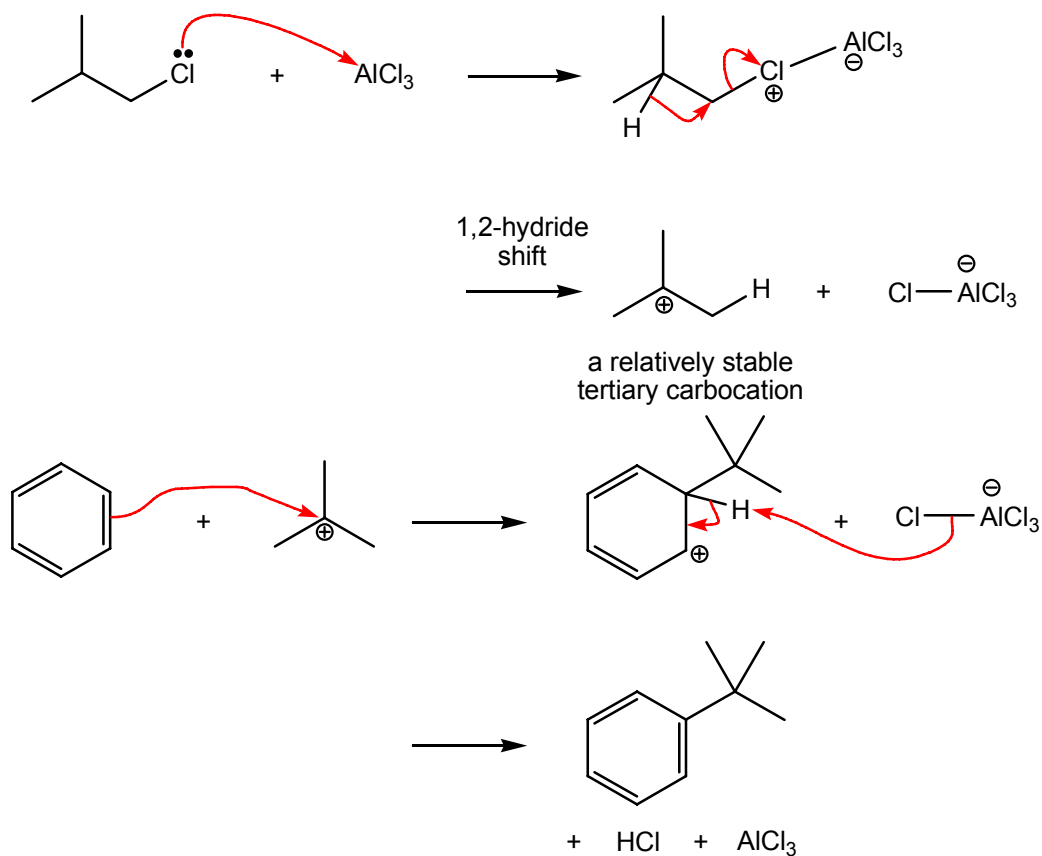
This reaction involves a Friedel–Crafts alkylation of benzene.

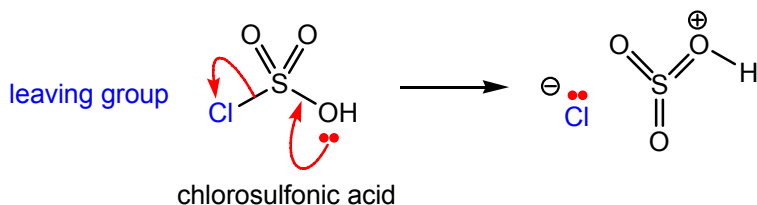


Activation of 1-chloro-2-methylpropane **A** with AlCl_3 (to give **B**), followed by loss of chlorine, forms the unstable primary carbocation **C** and AlCl_4^- . This primary carbocation, **C**, must rearrange to give the more stable tertiary carbocation **D** faster than electrophilic addition to benzene, as the product of this reaction, *tert*-butylbenzene **E**, is derived from this rearranged cation **D**.

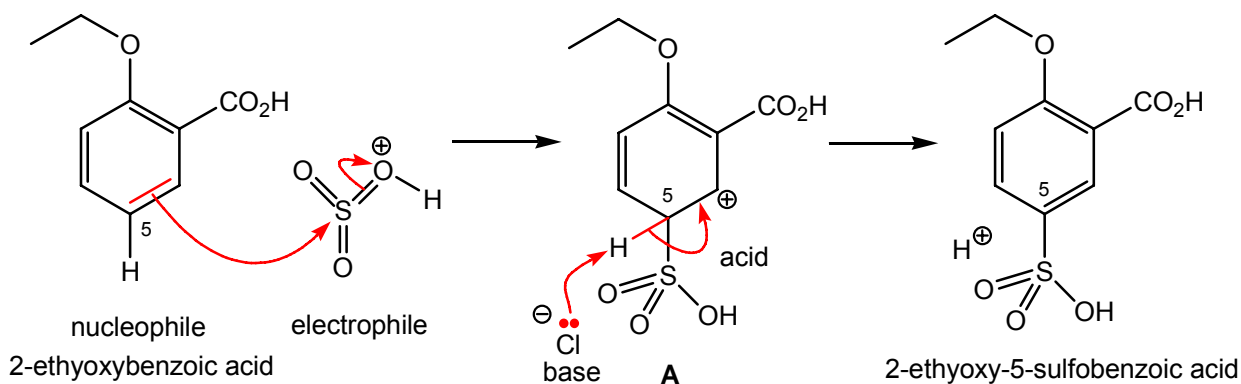


Answer

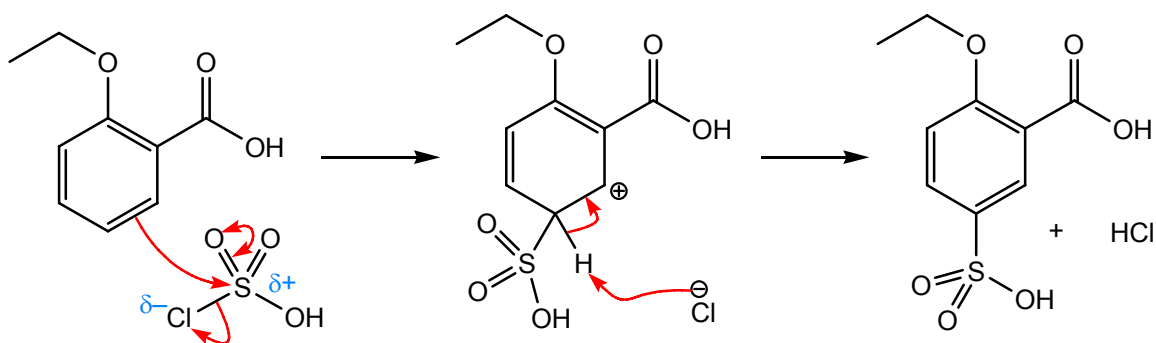




Regioselective addition of this electrophile, SO_3H^+ , to carbon-5 of 2-ethoxybenzoic acid forms to the intermediate conjugated carbocation, **A**; simple deprotonation with chloride gives the more stable aromatic 2-ethoxy-5-sulfobenzoic acid.



Answer



- (b) In 2-ethoxybenzoic acid, the EtO and CO_2H groups direct an incoming electrophile to the 3- and 5-positions of the ring. Suggest an explanation as to why the SO_3H group is selectively introduced at the 5-position, rather than the 3-position, of this ring.

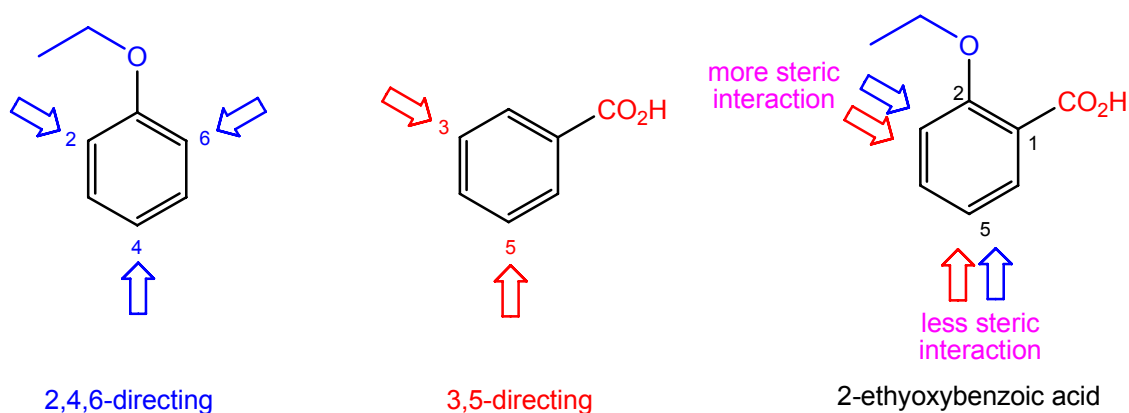
Strategy

Work out if the reaction involves electrophilic or nucleophilic substitution. Identify each substituent, and work out its directing ability. Determine the cumulative directing effect of

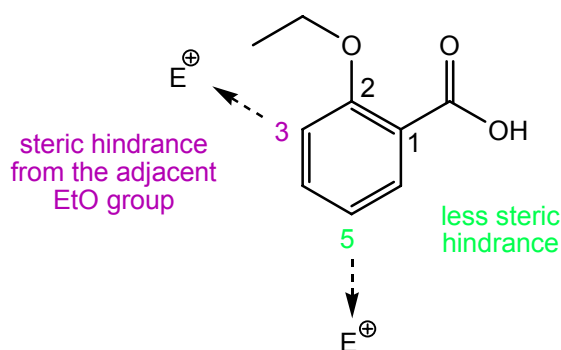
these substituents. Explain why the sulfonic acid group is selectively introduced at carbon-5, rather than the carbon-3 of 2-ethoxybenzoic acid.

Solution

This reaction involves electrophilic substitution of 2-ethoxybenzoic acid (nucleophile) using SO_3H^+ as the electrophile; carbon-5 of this aromatic ring appears to be the most nucleophilic carbon atom. The ethoxy (EtO) group is 2,4,6-directing, and the carboxylic (CO_2H) acid is 3,5-directing; cumulatively, the more nucleophilic positions are carbons-3 and -5 of 2-ethoxybenzoic acid as shown below. However, carbon-5 is more reactive than carbon-3 as it is less steric demanding (lower steric hindrance).

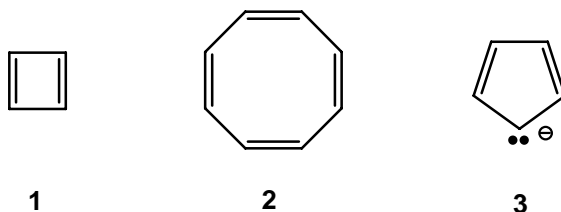


Answers



Answers to end of chapter questions (on p. 1044 in *Chemistry*³)

1. State Hückel's rule, and use it to predict which of the compounds **1–3** are aromatic.

Strategy

In order to determine whether these molecules are aromatic using Hückel's rule, you must work out if these molecules are cyclic, planar, contains uninterrupted (continuous) conjugation, and $(4n + 2)$ π -electrons. In some cases, it is a good idea to make a model to see if they are planar.

Solution

Hückel's rule states that a molecule is aromatic if it is cyclic, planar, contains uninterrupted (continuous) conjugation and $(4n + 2)$ π -electrons.

Cyclobutadiene **1** is not aromatic, as it does not obey the $(4n + 2)$ π -electron rule. It is **anti-aromatic** as it is cyclic, planar, contains uninterrupted (continuous) conjugation and has $4n$ π -electrons (where $n = 1$).

Cyclooctatetraene is not aromatic, as it is not planar (make a **model** to convince yourself), does not have uninterrupted (continuous) conjugation, and does not obey the $(4n + 2)$ π -electron rule. It is neither anti-aromatic even though it appears to have 8 π -electrons, as it is not planar and has no uninterrupted (continuous) conjugation. It is simply a tetraalkene.

Cyclopentadienyl anion is aromatic, as it is cyclic, planar, has uninterrupted (continuous) conjugation and contains $(4n + 2)$ π -electrons (where $n = 1 \rightarrow 6$ π -electrons).

Answer

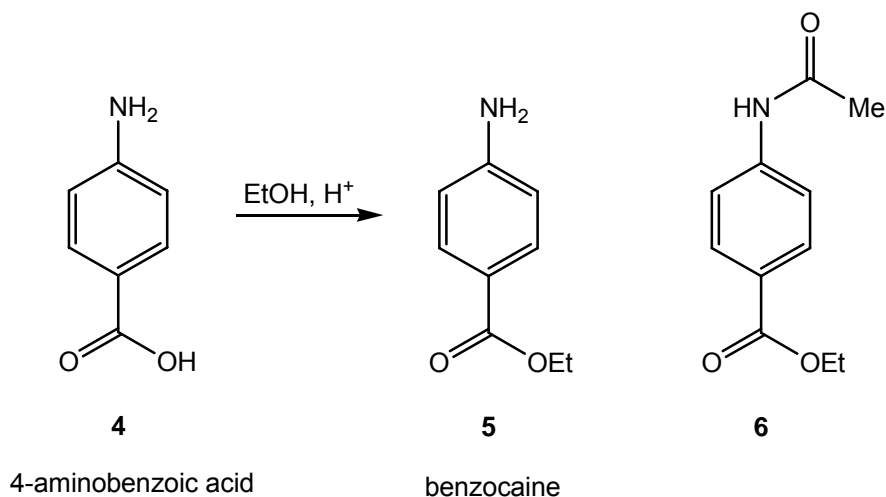
Hückel's rule states that aromatic compounds are monocyclic, planar and have an uninterrupted ring of $4n + 2$ π electrons (where $n = 1, 2, 3$ etc).

Compound **1** is monocyclic, planar and has an uninterrupted ring of 4 π electrons. It does not obey Hückel's rule and so it is not aromatic (it is anti-aromatic).

Compound **2** is monocyclic and has an uninterrupted ring of 8 π electrons. It does not obey Hückel's rule and it is not aromatic. (It is actually non-planar and non-aromatic, although this is not obvious from the structure drawn).

Compound **3** is monocyclic, planar and has an uninterrupted ring of 6 π electrons ($n = 1$). It obeys Hückel's rule and so it is aromatic.

3. Benzocaine **5** is a local anaesthetic, which is formed from 4-aminobenzoic acid **4**.



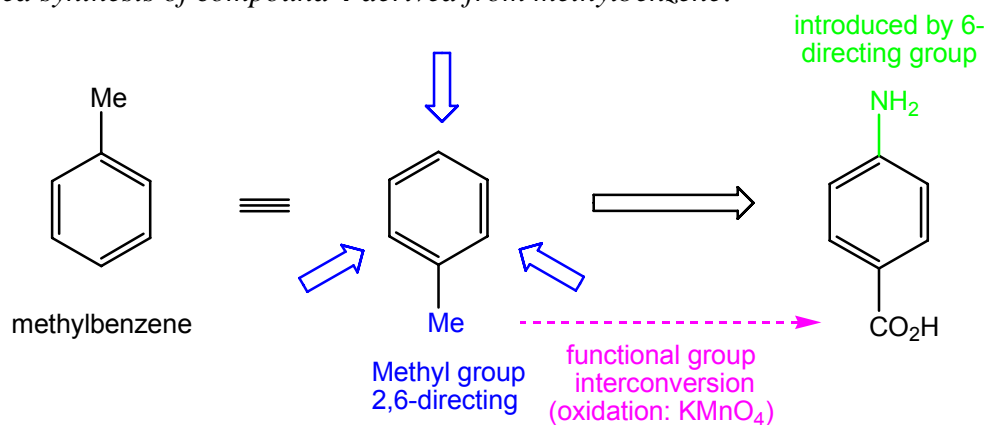
- (a) Suggest a three-step synthesis of **4** starting from methylbenzene. Comment on the regioselectivity of any electrophilic substitution reactions.

Strategy

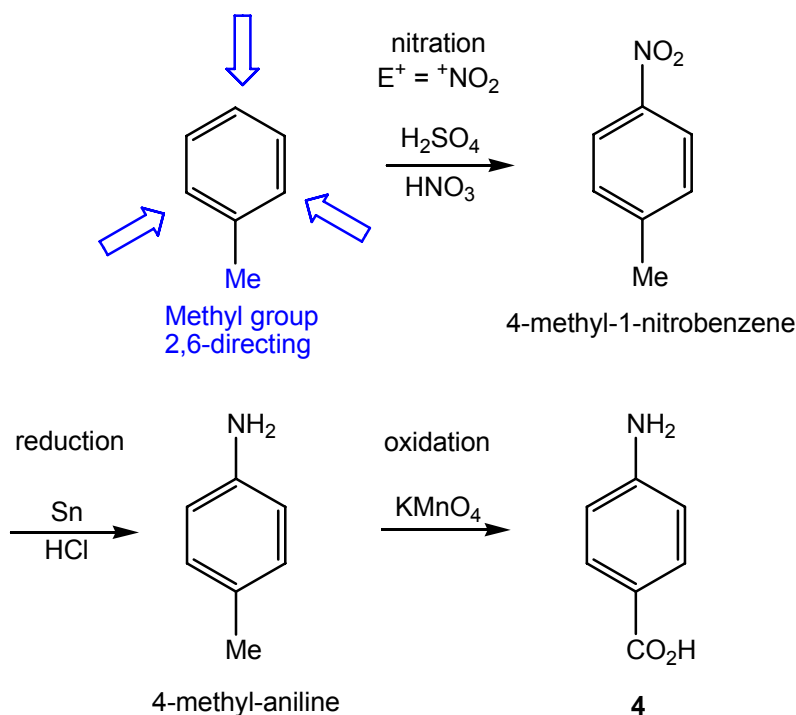
For each synthesis, draw out the starting material, label the substituent, and assign its directing effect. Work out if this directing effect and the newly introduced substituent is complementary. Suggest reagents for these required transformations.

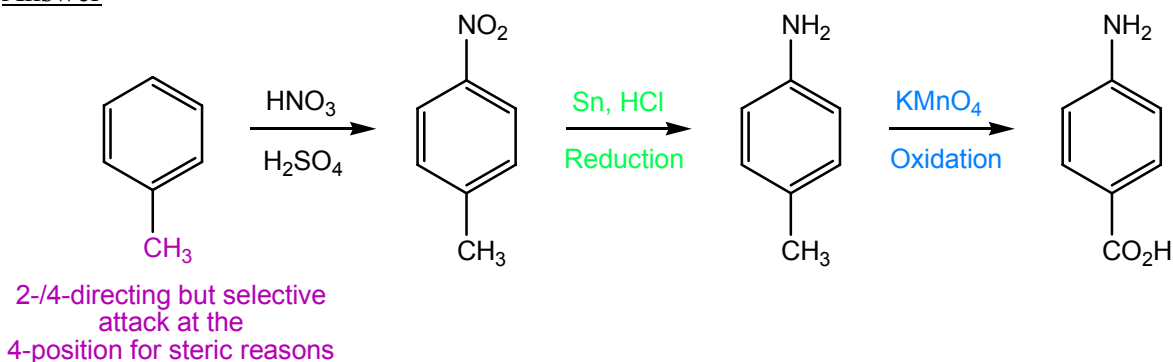
Solution

Proposed synthesis of compound **4** derived from methylbenzene.



In order to convert methylbenzene into compound **4**, the amino ($-\text{NH}_2$) group must be introduced into this molecule, before the methyl (Me) group is converted into the 3,5-directing carboxylic acid group. This amino group is introduced by nitration of methylbenzene ($\text{H}_2\text{SO}_4/\text{HNO}_3$) to give 4-methyl-1-nitrobenzene, followed by reduction (Sn/HCl) to give 4-methylaniline. Conversion of the methyl (Me) group (in 4-methylaniline) into the carboxylic acid (CO_2H) group (in **4**) can be achieved by oxidation using KMnO_4 . The proposed synthesis of compound **4**, starting from methylbenzene, is shown below.



Answer

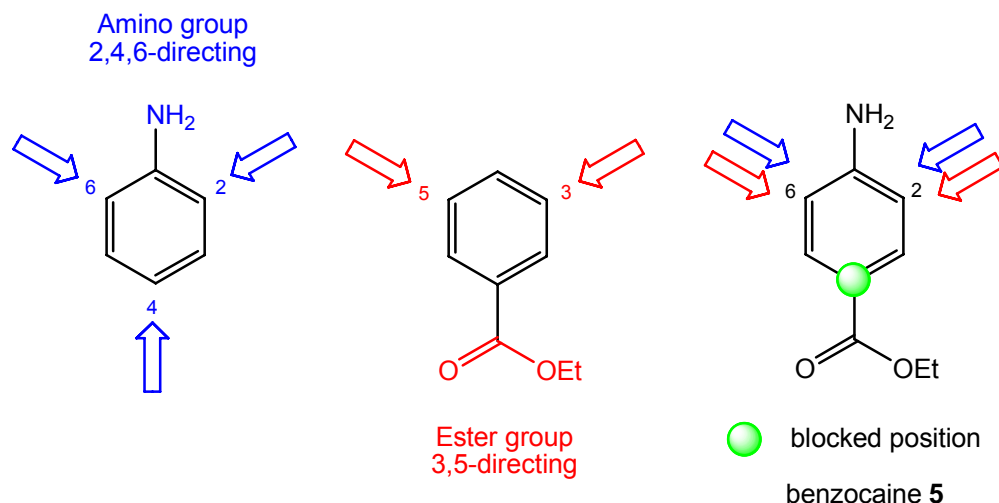
- (b) Which position of the ring in benzocaine **5** is most reactive towards an electrophile (E^+)? Explain your reasoning by drawing resonance forms of the carbocation reaction intermediates.

Strategy

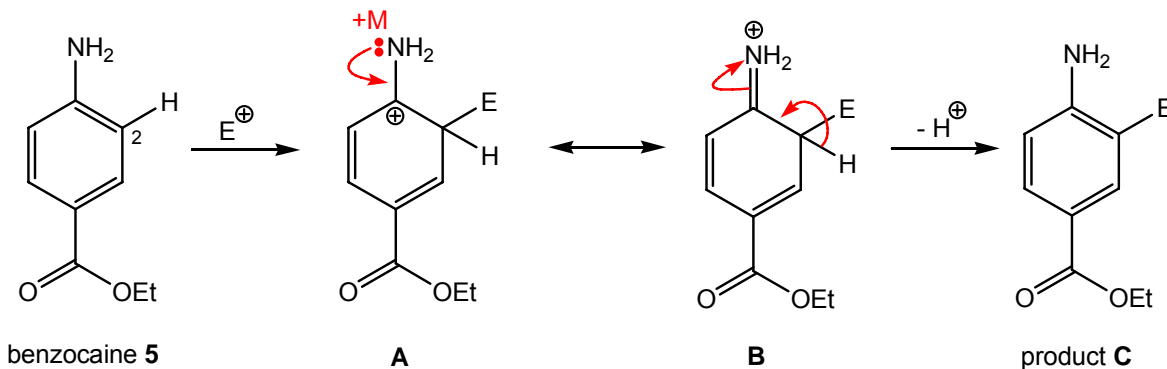
Work out if the reaction involves electrophilic or nucleophilic substitution. Identify each substituent, and work out its directing ability. Determine the cumulative directing effect of these substituents. Explain your reasoning by drawing resonance forms of the carbocation reaction intermediates.

Solution

The proposed reaction involves electrophilic substitution of benzocaine **4** (nucleophile) using an electrophile, E^+ ; carbons-2 and -6 of this aromatic ring appears to be the most nucleophilic carbon atom. The amino ($-NH_2$) group is 2,4,6-directing, and the ethyl ester (EtO_2C-) group is 3,5-directing; cumulatively, the more nucleophilic positions are carbons-2 and -6 of benzocaine **5** as shown below.



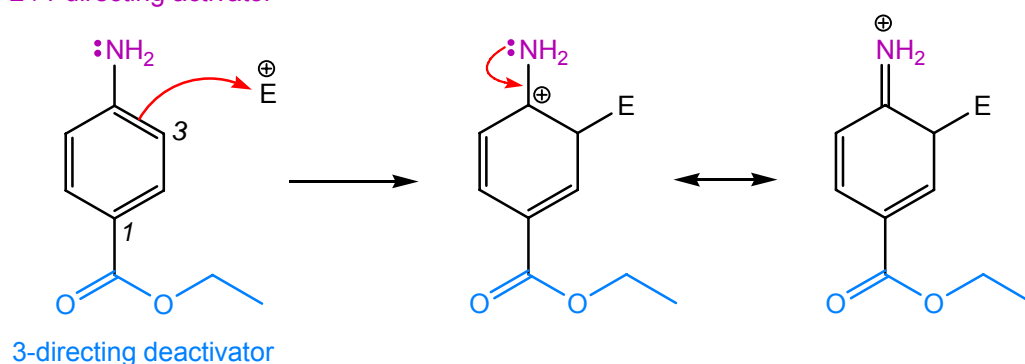
Electrophilic addition of E^+ to carbon-2 of benzocaine gives the intermediate conjugated carbocation **A**. This carbocation **A** can be resonance stabilised by the non-bonded pair of electrons on the neighbouring amino ($-NH_2$) group (to give the canonical structure **B**). Reformation of the more stable aromatic ring through deprotonation of **B** gives the 2-substituted benzocaine as the major product. The mechanism of this process is shown below.



Answer

Both the NH_2 and CO_2Et substituents direct the electrophile to the 3-position of the ring numbered below. Attack at the 3-position produces a carbocation, which is stabilised by the +M effect of the NH_2 substituent.

2-/4-directing activator



- (c) Would you expect benzocaine **4** or compound **6** to react more rapidly with an electrophile? Explain your reasoning.

Strategy

Work out if the reaction involves electrophilic or nucleophilic substitution. For each compound, benzocaine **4** and compound **6**, rationalise which is more or less nucleophilic (or electrophilic). Predict which compound would react faster with the given reagent (in this case, assume it is E^+).

Solution

These proposed reactions involve electrophilic addition of E^+ to the benzene rings of benzocaine **4** and compound **6**. Benzocaine **4** reacts more readily than compound **6**, as it is more nucleophilic (electron-rich) as the amino (NH_2 -) group (in **4**) has a stronger electron donating (+M) effect than the amide ($-NHCOMe$) group (in **6**).

Answer

Benzocaine **5** reacts more rapidly with electrophiles than compound **6**. The amino (NH_2 -) substituent is a stronger activating group than the $NHCOCH_3$ substituent, and it is also smaller, so electrophiles can more easily attack the 3-position of the ring.

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