Chem Factsheet

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The A-Level Chemistry of Benzocaine

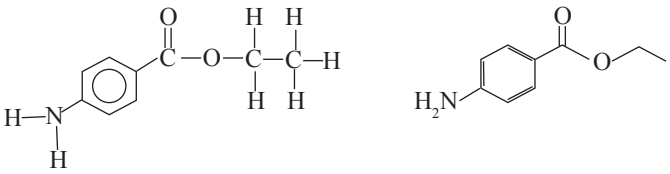
This Chem Factsheet is concerned with applying a range chemical principles and skills met at A-level to the benzocaine molecule. It is very much a synoptic exercise and might best be studied towards the end of an A-level course.

Benzocaine is a compound which acts as a local anesthetic and is commonly used as a pain reliever. It is the active ingredient in many ointments and drops for relieving pain from sunburn, oral ulcers, toothache, ear pain etc.

Benzocaine was first synthesized in 1890 by the German chemist Eduard Ritsert.

As shown in Fig.1, benzocaine is the ethyl ester of 4-aminobenzoic acid and is therefore named ethyl 4-aminobenzoate.

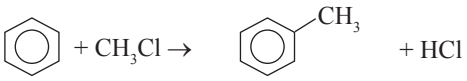
Fig. 1 : The full and skeletal structures of benzocaine



A Synthesis of Benzocaine from Benzene

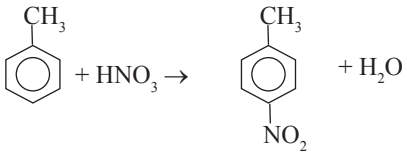
The scheme discussed is a multistep process but uses reactions studied in most A-level specifications.

Step 1: Conversion of benzene to methylbenzene by a **Friedel Crafts methylation** (substitution of a methyl group, CH_3). This is an electrophilic substitution by the methyl carbocation, $^+CH_3$. **Benzene is reacted with chloromethane using anhydrous aluminium chloride catalyst**.



Q1 Outline the mechanism for this reaction.

Step 2: Conversion of methylbenzene to 4-nitromethylbenzene by **nitration**. This is also an electrophilic substitution by the nitronium ion, $^+NO_2$. **Methyl benzene is reacted with concentrated nitric acid mixed with a concentrated sulphuric acid catalyst.**



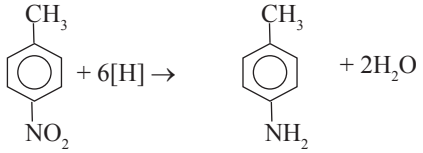
Q2 Outline the mechanism for this reaction.

Note: A significant amount of 2-nitromethylbenzene will also be produced. This would need to be separated from the 4-nitromethylbenzene before proceeding to step 3.

Q3 Suggest a technique for achieving this separation and purification. The melting and boiling temperatures are 52°C and 238°C for 4-nitromethylbenzene but -10°C and 222°C for 2-nitromethylbenzene.

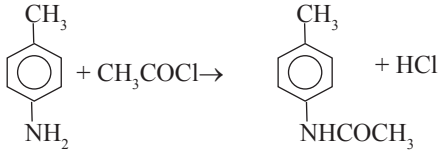
Q4 In terms of inter-molecular forces, suggest why the melting temperature of 2-nitromethylbenzene is so much lower than 4-nitromethylbenzene.

Step 3: **Reduction** of 4-nitromethylbenzene to 4-aminomethylbenzene. **4-nitromethylbenzene is reacted with moderately concentrated hydrochloric acid and tin.**



Note: This specialist reducing agent (Sn + HCl ≡ 6[H]) is necessary because use of, for example hydrogen and nickel, would also reduce the benzene ring to a cyclohexane derivative.

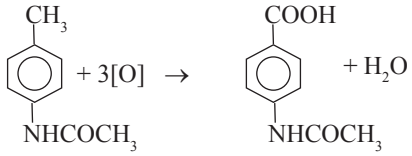
Step 4: Protection of the amino group in 4-aminomethylbenzene by **acylation**. This follows a nucleophilic addition-elimination mechanism and produces an N-substituted amide. **4-aminomethylbenzene is reacted with ethanoyl chloride**.



Note: This step is necessary because the amino group would otherwise be oxidised during step 5.

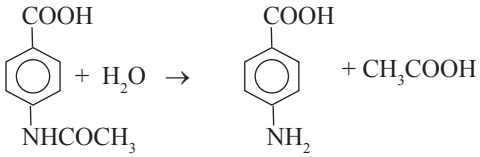
Q5 Outline the mechanism for this reaction.

Step 5: Conversion of the methyl group to a carboxylic acid group by **oxidation**. The N-substituted amide from step 4 is **refluxed with alkaline potassium manganate(VII) [$KMnO_4$] solution** (represented by [O]).



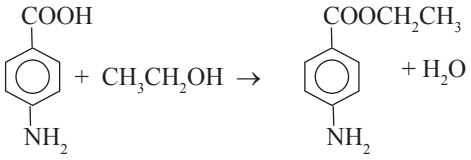
Note: This reaction is very general in that ANY carbon-based benzene side chain ($-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2Cl$ etc) is oxidised by alkaline manganate(VII) to a COOH group with additional C atoms being eliminated as carbon dioxide.
e.g. $C_6H_5CH_2CH_3 + 6[O] \rightarrow C_6H_5COOH + 2H_2O + CO_2$

Step 6: Removal of the acyl protecting group by **hydrolysis** to give 4-aminobenzoic acid. The product from step 5 is **refluxed with dilute hydrochloric acid**.



Note: The hydrochloric acid catalyses this reaction with water.

Step 7: Conversion of 4-aminobenzoic acid to ethyl 4-aminobenzoate (benzocaine) by **esterification**. This involves **4-aminobenzoic acid being heated with ethanol in the presence of a concentrated sulphuric acid catalyst**.



Confirmation of Structure

Having completed this synthesis and purification of benzocaine, it is necessary to confirm that the product does in fact have the expected structure. This is best done using spectroscopy but other techniques might be applied.

1. Melting Point Determination

The value should be 89-90°C if the sample is benzocaine. However, this is not confirmation because other molecules may have the same melting point. More importantly, the purity of the sample is indicated. A small amount of impurity will cause the melting point to be lower and occur over a much wider range.

2. Chromatography

Thin layer chromatography (tlc) or paper chromatography can be used to indicate the purity of the sample. A pure sample will produce only one "spot" after being subjected to these techniques using a variety of solvents. Comparing the R_f value of the "spot" with that of an authentic sample of benzocaine can also give evidence about the identity of the sample.

Rem. R_f = Distance travelled by "spot"/ Distance travelled by solvent.

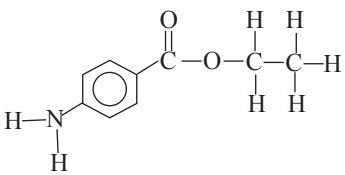
Gas chromatography can also be used. A single "peak" will suggest the sample is pure and comparing the retention time of the "peak" with that of an authentic sample of benzocaine can also give evidence about the identity of the sample.

3. Infra-Red Spectroscopy

Infrared Absorption Data

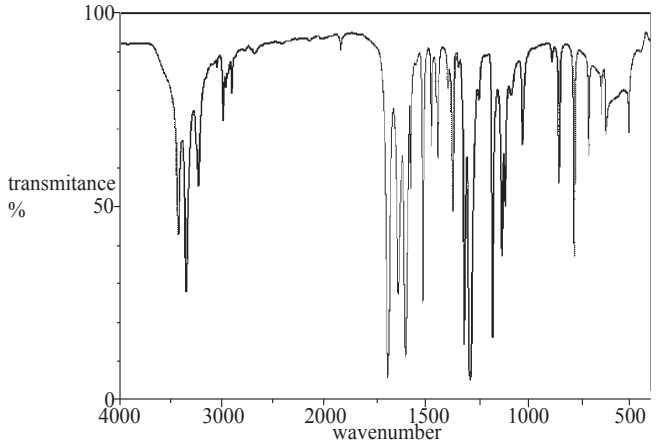
Bond	Absorption range (/cm^{-1})	Bond	Absorption range (/cm^{-1})
N-H (amine)	3300 – 3500	O-H (alcohol)	3230 – 3550
C-H	2850 – 3300	O-H (acid)	2500 – 3000
C≡N	2220 – 2260	C=O	1680 – 1750
C=C	1620 – 1680	C-O	1000 – 1300
C-C	750 – 1100	C-N	1020 – 1220

Benzocaine



Q6 Which absorptions would be expected in the IR spectrum of benzocaine?

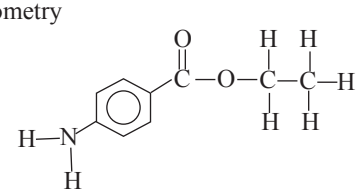
Q7 How many of these expected absorptions are seen in the spectrum shown below?

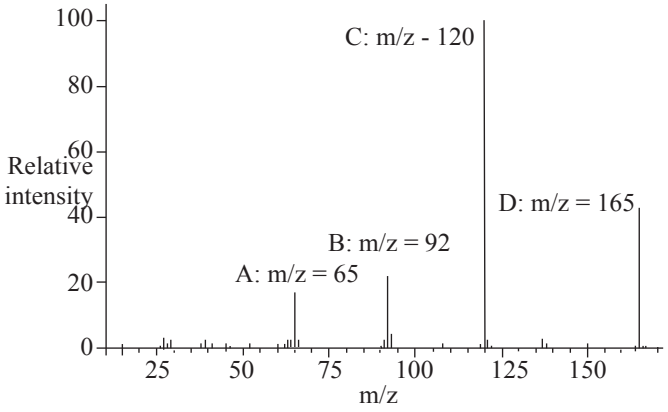


Q8 How could this spectrum best be used to show that a prepared sample is, or is not, benzocaine?

4. Mass Spectrometry

Benzocaine





Q9 Work out the molecular formula and relative molecular mass of benzocaine.

Q10 Identify as far as possible the species responsible for the production of each of the peaks A-D and write an equation for the formation of each in the mass spectrometer.

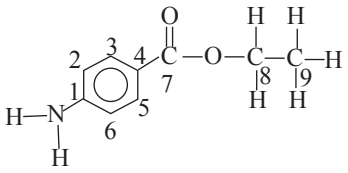
Q11 How could this spectrum be used to authenticate a prepared sample?

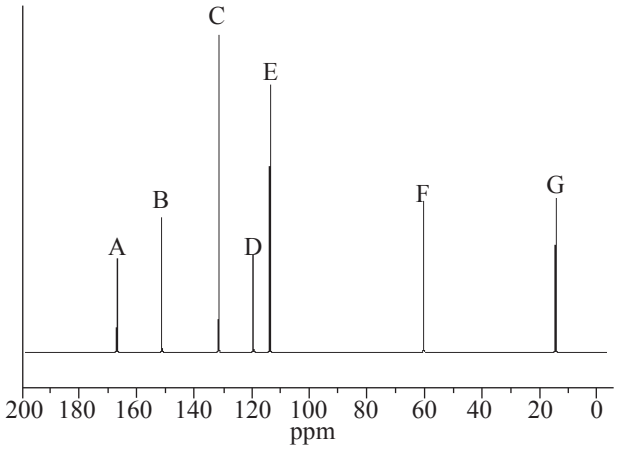
5. ^{13}C NMR Spectroscopy

Q12 As seen on page 3, the benzocaine molecule contains 9 carbon atoms. Explain why the ^{13}C nmr spectrum contains only 7 absorptions.

Q13 Using the data table below assign absorptions A-G to the appropriate carbon atoms from 1-9.

Benzocaine

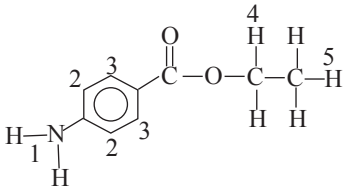


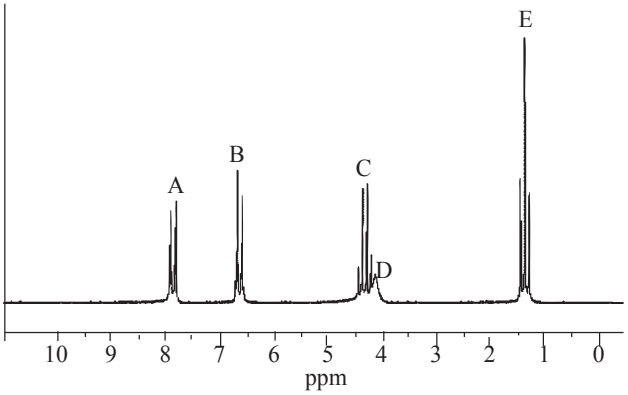


Type of **C**	Group	δ / ppm
C-**C**	Alkyl	5 - 40
R-**C**-NH_2	Amine	25 - 60
R-**C**-O	Alcohol, ester, ether	50 - 90
R-**C**OO-	Ester, acid	160 - 185
$\mathbf{C}_6H_5$-	Aryl	110 - 160

6. ^{1}H NMR Spectroscopy

Benzocaine





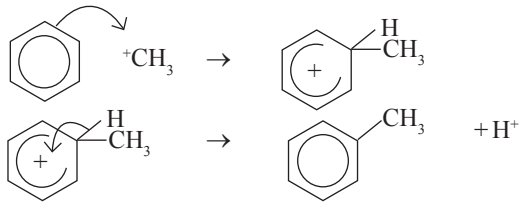
Type of **H**	Group	δ / ppm
R-C**H**	Alkyl	0.7 – 1.4
R-N$\mathbf{H}_2$	Amine	1.0 – 4.5
R-CO-C**H**	Ketone	2.1 – 2.6
R-COO-C**H**	Ester	3.7 – 4.1

Q14 The 5 different groups of equivalent protons are labelled 1-5 in the structure shown above. Assign each of the absorptions A-E in the proton spectrum to one of the proton groups 1-5.

Q15 Explain why (a) absorption A is a doublet
(b) absorption B is a doublet
(c) absorption C is a quartet
(d) absorption D is a singlet
(e) absorption E is a triplet

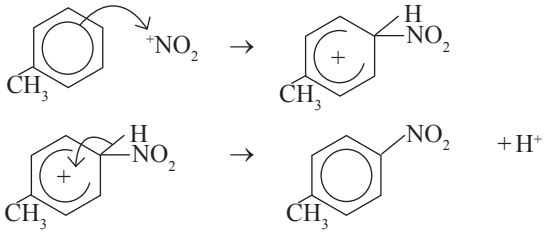
Answers

Q1 $CH_3Cl + AlCl_3 \rightarrow {}^+CH_3 + AlCl_4^-$



$H^+ + AlCl_4^- \rightarrow HCl + AlCl_3$

Q2 $HNO_3 + 2H_2SO_4 \rightarrow {}^+NO_2 + 2HSO_4^- + H_3O^+$

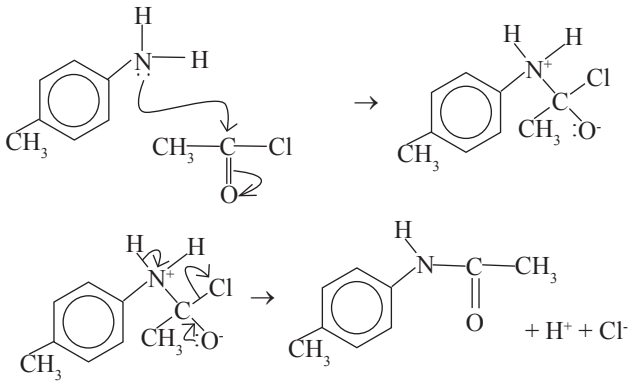


$H^+ + HSO_4^- \rightarrow H_2SO_4$

Q3 Large scale column chromatography is probably the best technique. This is a non-destructive technique. Fractional distillation at reduced pressure (to reduce the boiling temperatures) might also be used.

Q4 The 4-nitromethylbenzene molecule is much more symmetrical than 2-nitromethylbenzene. This means the inter-molecular forces (dipole-dipole forces and van der Waals forces) are more effective because the more symmetrical molecules can pack more closely together.

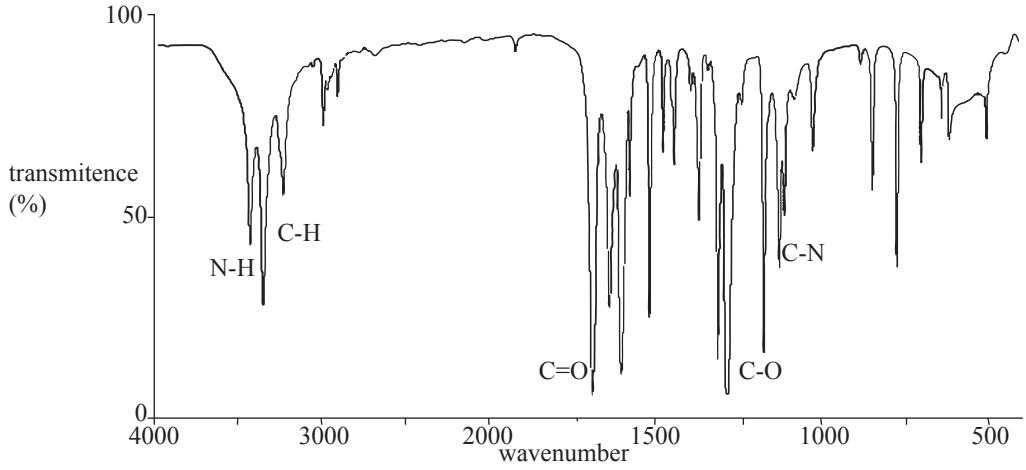
Q5



Q6 N-H (3300 – 3500 cm^{-1}), C-O (1000 – 1300 cm^{-1}), C=O (1680 – 1750 cm^{-1}), C-N (1020 – 1220 cm^{-1}) and C-H (2850 – 3300 cm^{-1})

Q7 All absorptions seem to be present but exact allocation is difficult!

Q8 Compare it with the IR spectrum of an authentic sample of benzocaine. There should be an exact match if the experimental sample is benzocaine. This can be done using automated comparison via a computerised database, especially comparing the "fingerprint regions"



of the spectra – the absorptions occurring at below 1500cm^{-1}.

Q9 $C_9H_{11}NO_2 \rightarrow 9(12) + 11(1) + 14 + 2(16) = 165$

Q10 D: Molecular ion radical $[C_9H_{11}NO_2]^{\bullet+}$
$C_9H_{11}NO_2 \rightarrow [C_9H_{11}NO_2]^{\bullet+} + e^-$

A: No single bond fission can produce this fragment. Empirically it could be $[C_4H_3N]^+$ or $[C_4HN]^+$ etc but these must involve multiple bond fissions and possibly recombination which is beyond A-level.
B: Fragment from C to benzene ring fission, $[C_6H_6N]^{\bullet+}$
$[C_9H_{11}NO_2]^{\bullet+} \rightarrow [C_6H_6N]^+ + [C_3H_5O_2]^{\bullet}$
C: Fragment from C-O fission, $[C_7H_6NO]^{\bullet+}$
$[C_9H_{11}NO_2]^{\bullet+} \rightarrow [C_7H_6NO]^+ + [C_2H_5O]^{\bullet}$

Q11 As with IR spectra, compare this authentic spectrum with the mass spectrum of the prepared sample of benzocaine. There should be an exact match if the experimental sample is benzocaine. This can also be done using automated comparison via a computerised database.

Q12 Carbon atoms 2 and 6 have the same molecular environment and produce only one absorption. Similarly, carbon atoms 3 and 5 produce only one absorption.

Q13 A–7 ; B–1 ; C–3&5 (2x intensity) ; D–4 ; E–2&6 (2x intensity) ; F–8 ; G–9.

Q14 A–3 ; B–2 ; C–4 ; D–1 ; E–5

Q15 (a) 1 H (group 3) on neighbouring carbon → 1+1 split → doublet
(b) 1 H (group 2) on neighbouring carbon → 1+1 split → doublet
(c) 3 H (group 5) on neighbouring carbon → 3+1 split → quartet
(d) 0 H on neighbouring carbon → 0+1 split → singlet
(e) 2 H (group 4) on neighbouring carbon → 2+1 split → triplet

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