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7. Following a synthetic route

The spectroscopic techniques discussed in this book can be used to assess the purity of compounds. It is also possible to monitor the progress of a reaction from the data obtained on the reagents and/or products of the reaction. Although this can sometimes be achieved by using one technique alone, more conclusive evidence can be gained from using several techniques.

The purpose of this chapter is to show how spectra change as a molecule is modified in a chemical synthesis, including the data from mass, infrared, and NMR spectral investigations. A book could be devoted to the interpretation of these spectra alone, so some of the important peak assignments have been given and a brief discussion has been included.

The target molecule is Ibuprofen (a drug invented and marketed by Boots Pharmaceuticals). Details of the synthesis are given in the Box.

All of the compounds are liquids at room temperature and pressure except Ibuprofen which is a solid. The mass spectra were all obtained by 70 eV (6750 kJ mol^{-1}) EI using a probe temperature of 150 °C; the infrared spectra were obtained from liquid films, except ibuprofen which was obtained from a KBr disc; and the NMR spectra were obtained from solution in deuterated trichloromethane, $CDCl_3$, using a 90 MHz instrument.

Isobutyl benzene

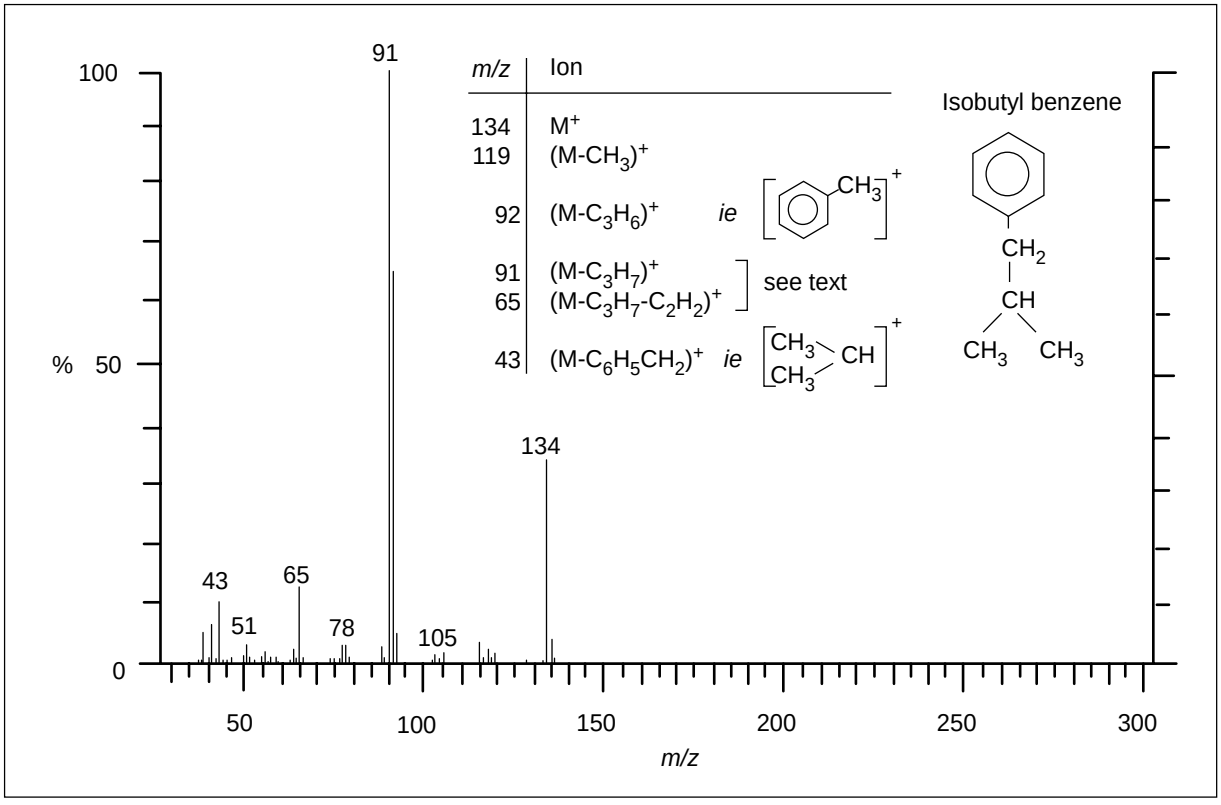

Figure 1 Mass spectrum of isobutyl benzene

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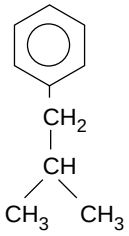
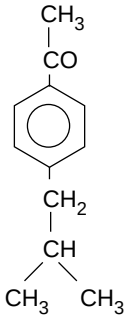
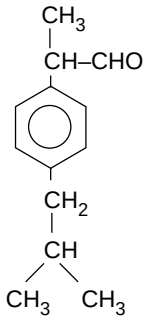
Methyl propyl benzene (isobutyl benzene) is used as the starting material.



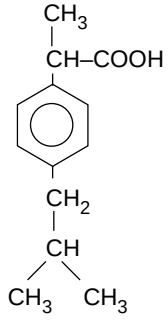
This undergoes a Friedel-Crafts acylation to give 4-isobutyl acetophenone.



This is converted via a Darzen's condensation to 2,(4-isobutylphenyl) propionaldehyde.



Which is oxidised to ibuprofen, 2,(4-isobutylphenyl) propanoic acid.



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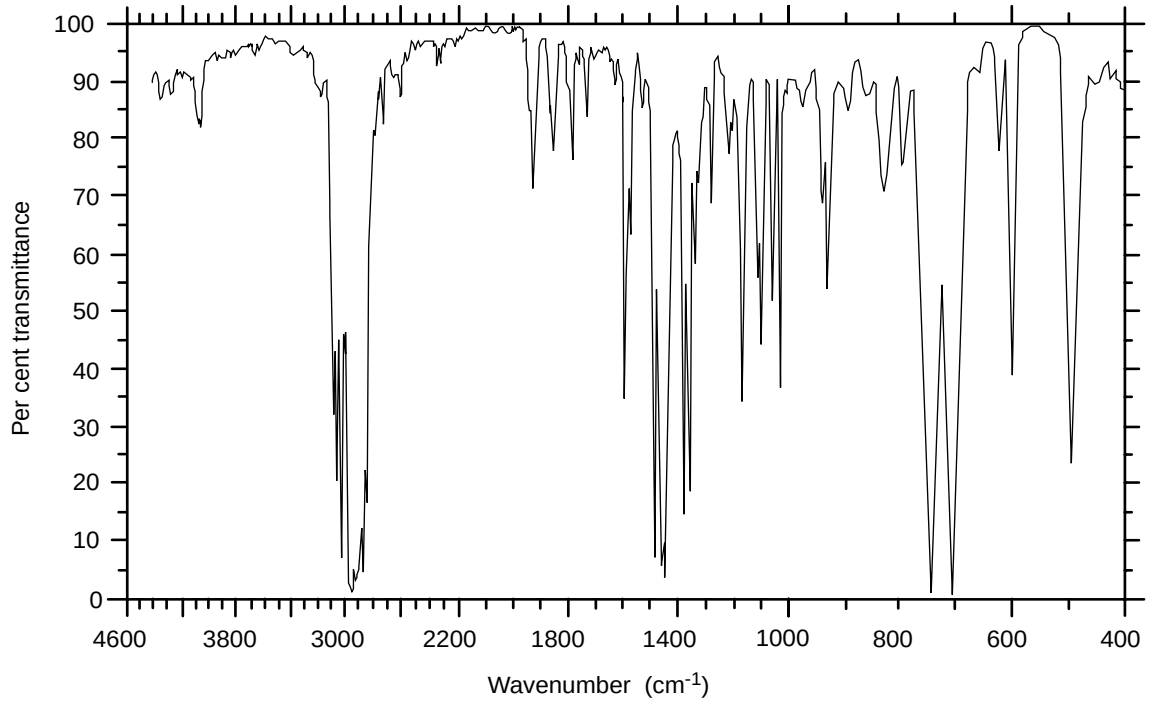
The major feature of this spectrum is the ease with which the link one bond away from the benzene ring is broken. Although methyl groups are fragmented, giving a peak at (M-15)=119, and there is loss of C_3H_6 (m/z = 92) – the most abundant peak is at m/z = 91. This corresponds to loss of the $(CH_3)_2CH$- group, to give $C_7H_7^+$ which rearranges as:

It is known as the tropyllium ion and loses C_2H_2 readily to give a relatively stable five membered ring with m/z = 65:

The ions of these seven- and five-membered rings are also detected in the mass spectra of ibuprofen and its intermediates.



ν cm^{-1}	
3100–3040	Aromatic C–H stretch
2980–2840	Alkane C–H stretch
1960–1740	C–H out of plane bending overtone and combination band
1610	C=C aromatic stretch
1470	Scissor of CH_2 hydrogen atoms
1455	Asymmetric C–H stretch of CH_3 groups
1170	Skeletal vibration of $-CH(CH_3)_2$
735, 700, 500	C–H out of plane deformation and out of ring deformation of a monosubstituted benzene

Isobutyl benzene

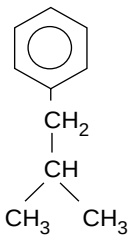


Figure 2 Infrared spectrum of isobutyl benzene

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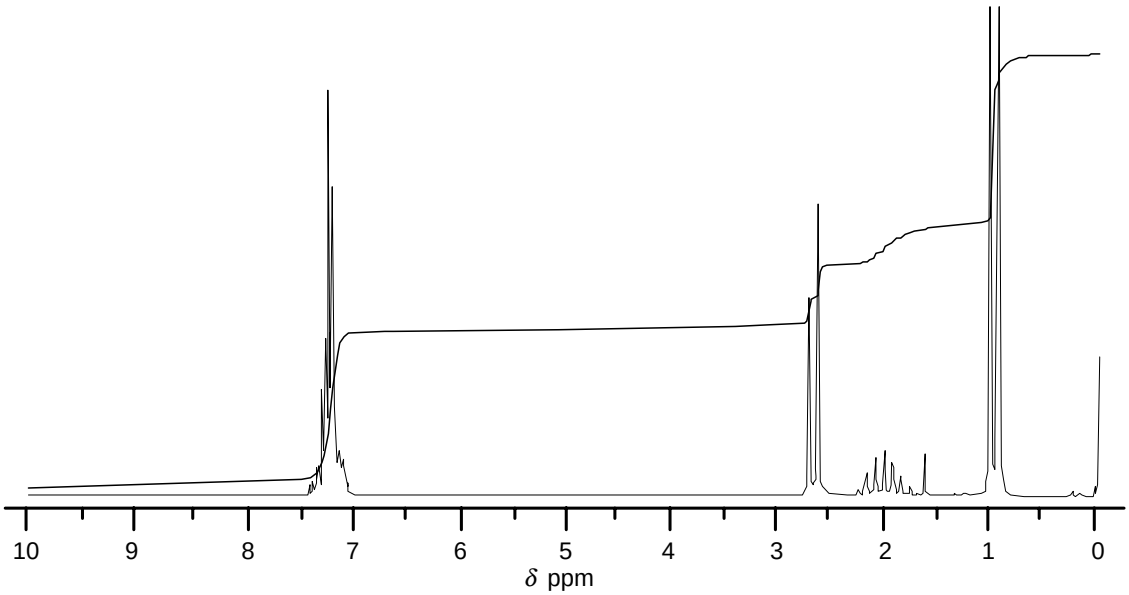
Because this molecule is a hydrocarbon, it is not surprising that its infrared spectrum is dominated by the vibrational modes of the C–H, C=C and C–C bonds. Some of these are assigned on the spectrum.



δ ppm	Peak	Integration	Protons
7.3	Multiplet	5	aromatic ring protons C–H^d
2.6	Doublet	2	CH_2^c
1.9	Multiplet	1	CH^b
1.7	Singlet	–	Water
0.9	Doublet	6	CH_3^a

Isobutyl benzene

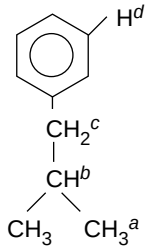


Figure 3 NMR spectrum of isobutyl benzene

The assignment of peaks is quite straightforward in this case. They are well separated and contain simple splitting patterns. The peak for the methine proton (*b*) is really a septet of triplets, because the proton couples with the two methylene protons (*c*) and the six (equivalent) methyl protons (*a*). The splitting is not clear owing to peak overlap. Because the alkyl side chain of the molecule is unchanged throughout the synthesis all of its protons should give the same peaks in all the NMR spectra. This is found to be the case. As expected, the resonance of the ring protons is seen at a chemical shift of *ca* $\delta = 7.3$.

An unexpected peak appears at δ = *ca* 1.7. This is due to water.

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4-isobutyl acetophenone

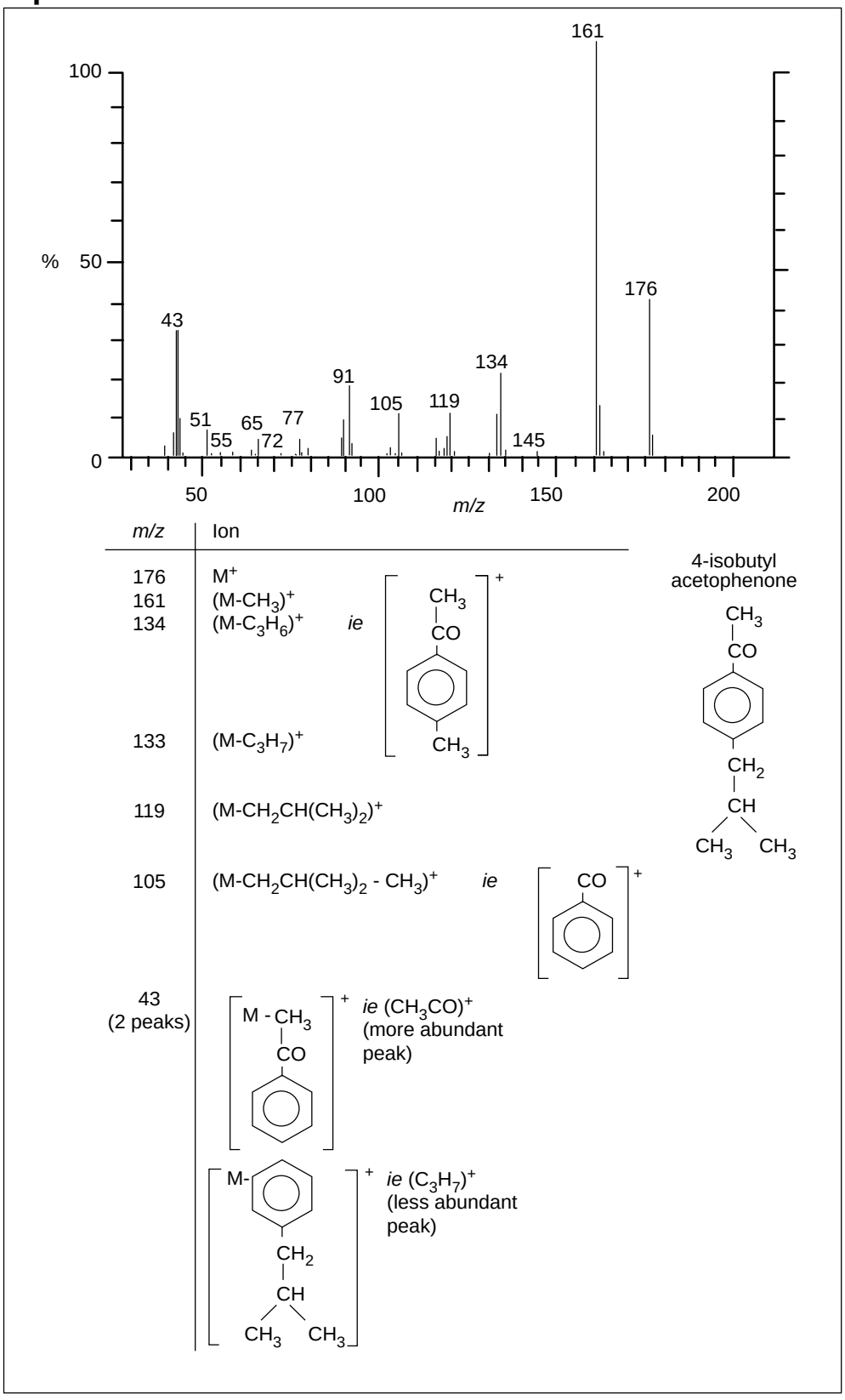

Figure 4 Mass spectrum of 4-isobutyl acetophenone

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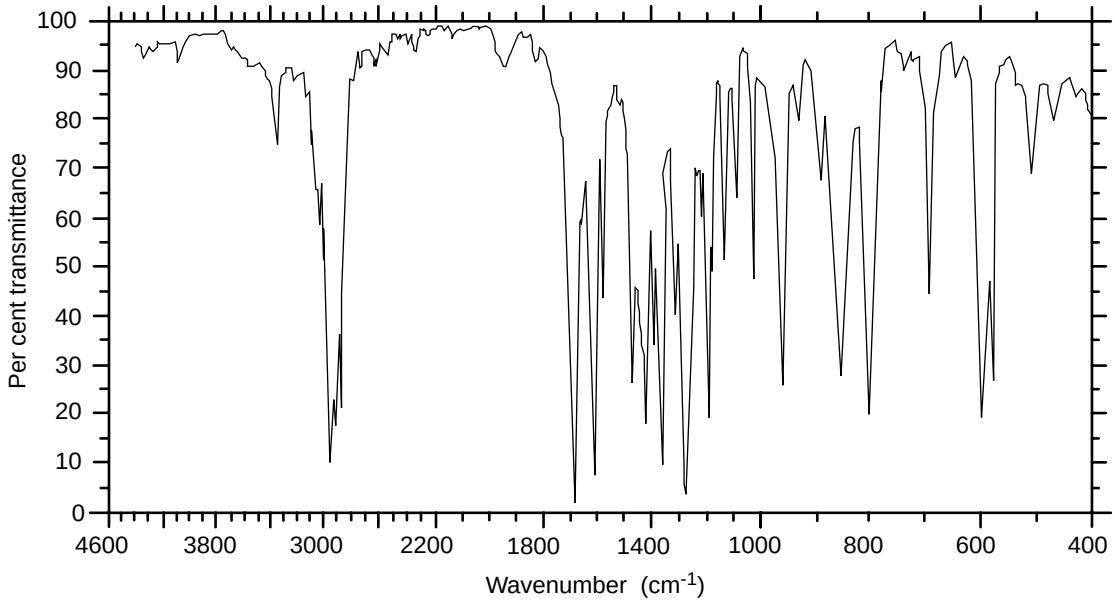
An ethanoyl group has been put in the ring position *para* to the alkyl side chain, and the mass spectrum now shows a particularly stable ion at m/z = 161 (M-15) if a methyl group is cleaved off.

The spectrum also shows that the bonds between the carbonyl group and the benzene ring; and the C–C bond between the CH_2 and CH groups are susceptible to cleavage. In both cases the charge can be on either fragment, so both are observed. The smaller fragment in each case has $m/z \approx 43$, and these are seen as separate peaks in the spectrum because of the slight differences in the accurate masses of the ions.



ν cm^{-1}	
3360	C=O overtone
3100–3000	Aromatic C–H stretch
3000–2850	Alkyl C–H stretch
1960–1800	C–H out of plane bending overtone and combination band
1700–1680	Aromatic ketone C=O stretch
1610–1570	Conjugation of C=C and C=O
855	C–H out of plane deformation characteristic of a para disubstituted benzene

4-isobutyl acetophenone

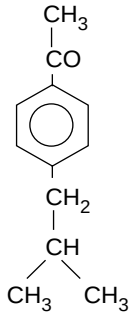


Figure 5 Infrared spectrum of 4-isobutyl acetophenone

The major difference between this spectrum and that of isobutyl benzene is the presence of the peak due to the aromatic ketone carbonyl at 1680 cm^{-1}. An overtone of this vibration is observed at twice this frequency, 3360 cm^{-1}. Two other peaks of interest are seen at 1570 and 1610 cm^{-1} – these are absorptions resulting from the conjugation of the carbonyl group with the unsaturated benzene ring.

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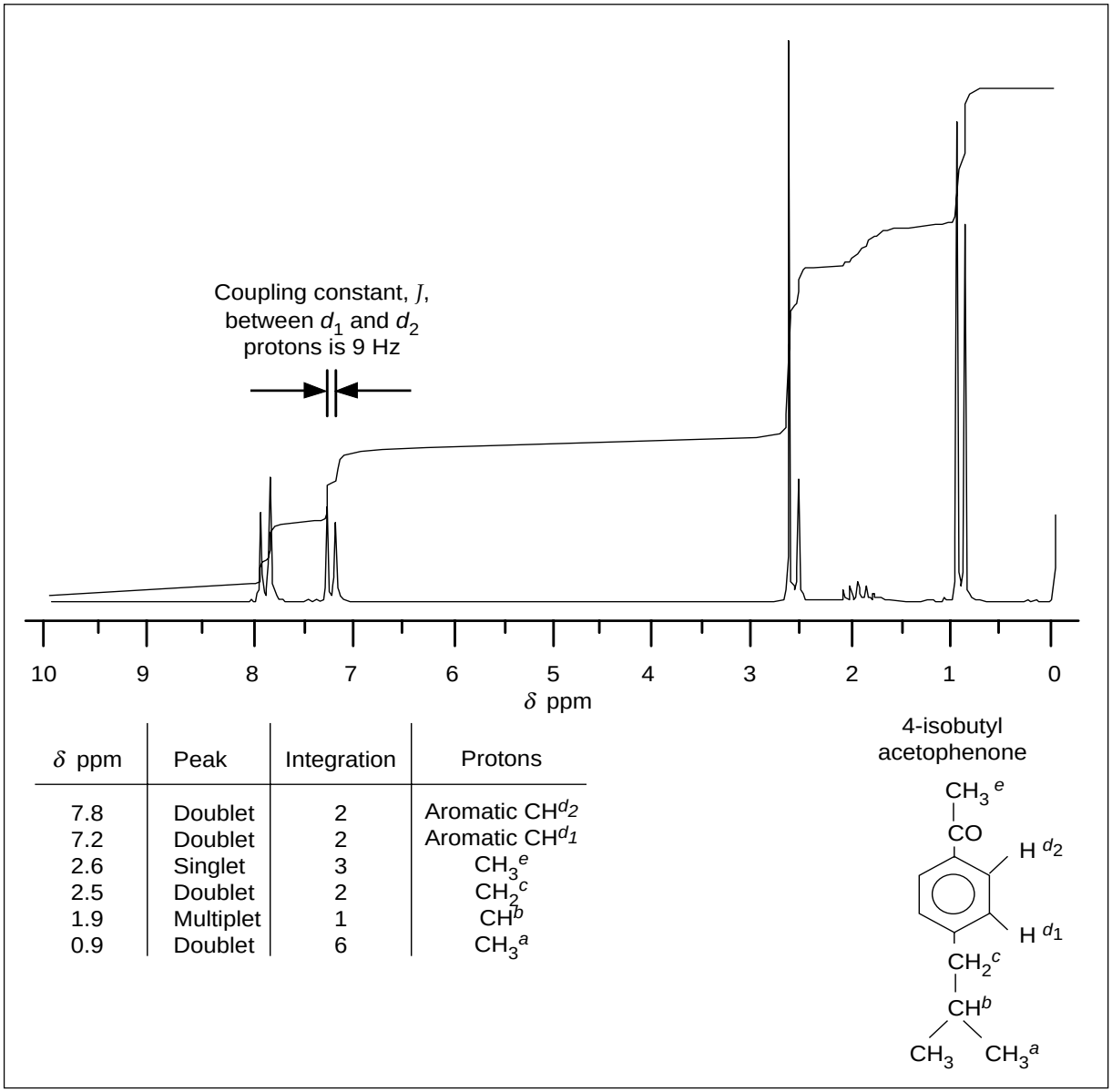

δ ppm	Peak	Integration	Protons
7.8	Doublet	2	Aromatic CH^{d_2}
7.2	Doublet	2	Aromatic CH^{d_1}
2.6	Singlet	3	CH_3^e
2.5	Doublet	2	CH_2^c
1.9	Multiplet	1	CH^b
0.9	Doublet	6	CH_3^a

4-isobutyl acetophenone

Figure 6 NMR spectrum of 4-isobutyl acetophenone

Adding the ethanoyl group to the molecule has two effects on the NMR spectrum:

1 a singlet appears at $\delta = 2.6$ – this is from the methyl group adjacent to the carbonyl and overlaps one of the lines of the methylene protons (*c*); and

2 the peak from the benzene ring protons is split into two doublets: an upfield doublet from the protons *ortho* to the alkyl side chain (d_1); and a downfield doublet at $\delta = 7.8$ from the protons ortho to the ethanoyl group (d_2) – these protons are more deshielded because of the presence of the electronegative oxygen. Measurement of the difference in frequency between the lines in each doublet gives the coupling constant between the d_1 and the d_2 protons. This pattern confirms that the ethanoyl group has been introduced in the para position.

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2,(4-isobutylphenyl) propionaldehyde

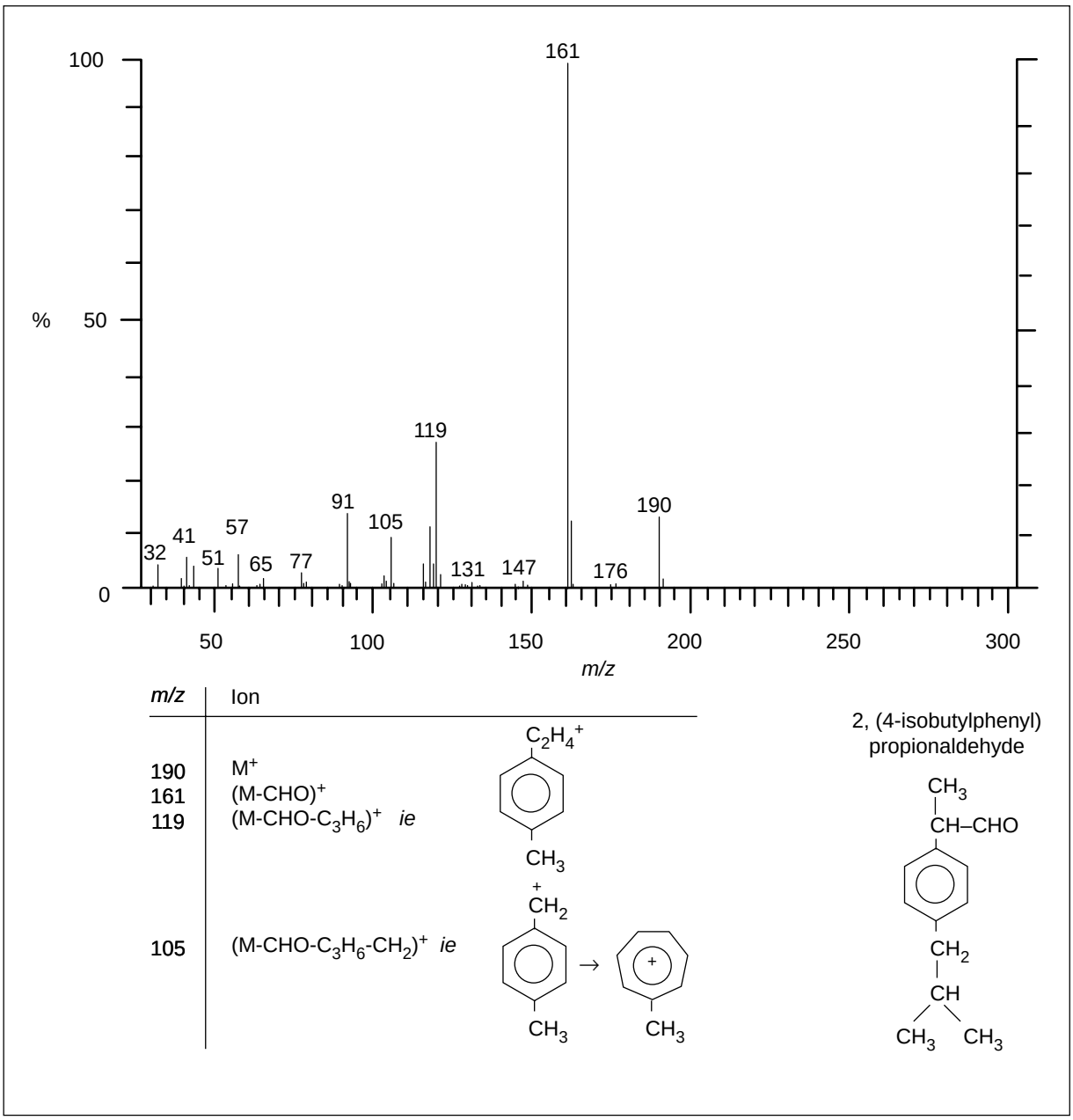

Figure 7 Mass spectrum of 2,(4-isobutylphenyl) propionaldehyde

After the Darzen's condensation the most significant peaks are due to the loss of the aldehydic group CHO at (M-29), and subsequent loss of a C_3H_6 group from the alkyl side chain at (M-71).

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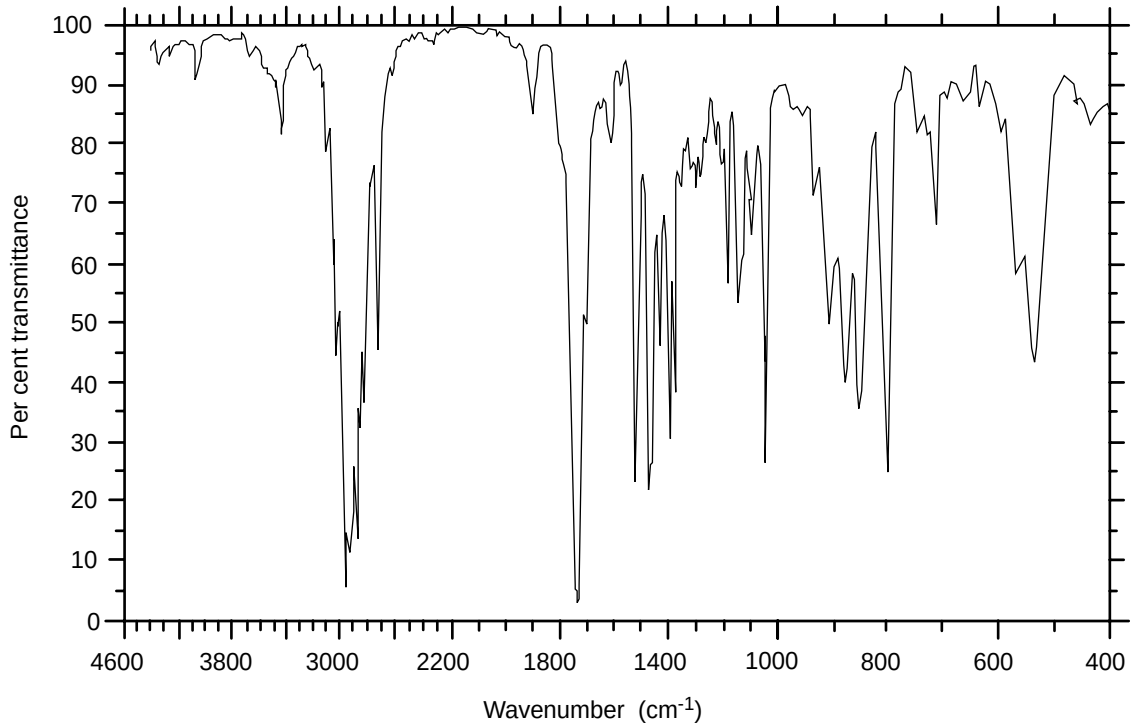

ν cm^{-1}	
3440	C=O overtone
3100–3000	Aromatic C–H stretch
3000–2800	Alkyl C–H stretch
2600	Aliphatic aldehyde C–H stretch
1905, 1780	C–H out of plane bending overtone and combination
1740–1720	Aliphatic aldehyde stretch C=O
860–800	Out of plane C–H deformation and out of ring deformation of para disubstituted benzene ring

2,(4-isobutylphenyl) propionaldehyde

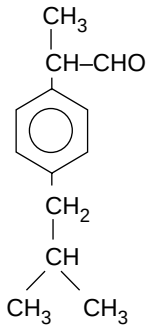

Figure 8 Infrared spectrum of 2,(4-isobutylphenyl) propionaldehyde

The absorptions due to the hydrocarbon vibrations are still present, but the carbonyl vibration has moved from 1680 cm^{-1} in the aldehyde to 1720 cm^{-1}. An overtone at twice this new carbonyl stretch frequency is again observed.

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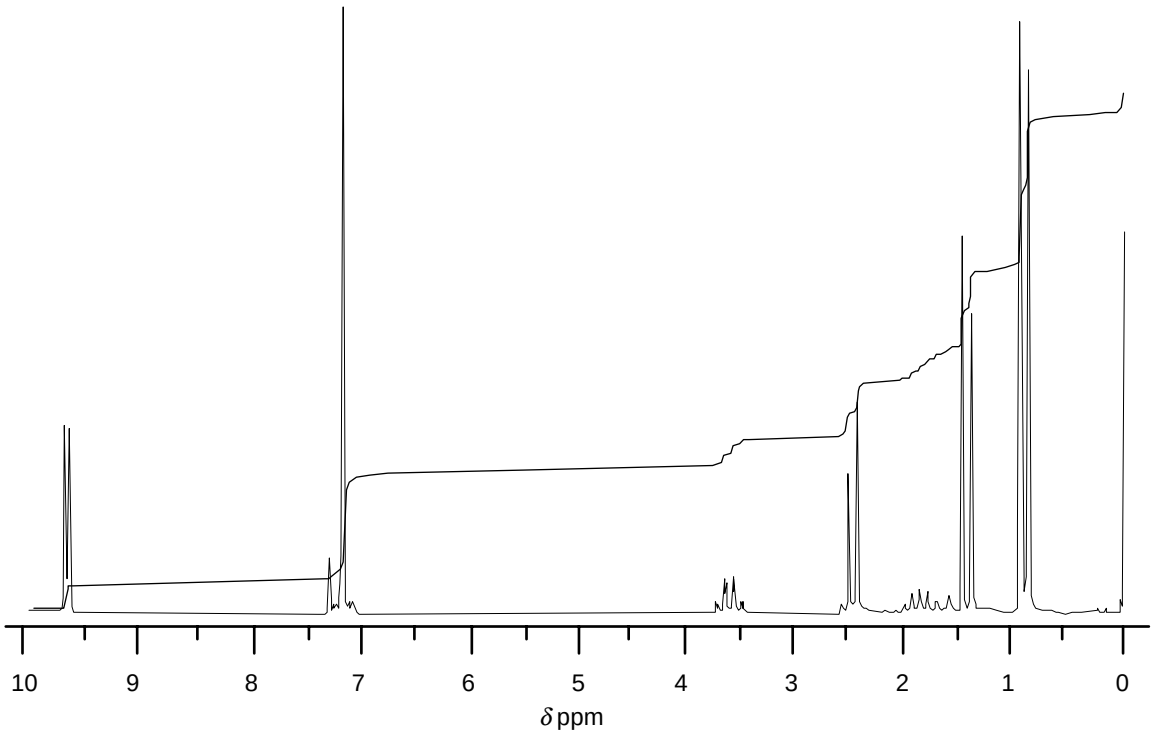

δ ppm	Peak	Integration	Protons
9.7	Doublet	1	CHO ^{g}
7.2	Singlet	4	aromatic CH^{d}
3.6	Quartet of doublets	1	CH^{f}
2.4	Doublet	2	CH_2^{c}
1.8	Multiplet	1	CH^{b}
1.6	Singlet	–	water
1.4	Doublet	3	CH_3^{e}
0.9	Doublet	6	CH_3^{a}

2,(4-isobutylphenyl) propionaldehyde

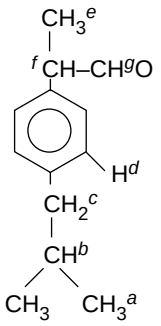

Figure 9 NMR spectrum of 2,(4-isobutylphenyl) propionaldehyde

The singlet from the methyl protons (*e*) has now expanded to a doublet and has moved upfield to $\delta = 1.4$ because of the proton (*f*) on the CH group now adjacent to it. The methine proton (*f*) gives a quartet of doublets as it couples with both the methyl protons (*e*) and the aldehydic proton (*g*). The aldehydic proton itself appears downfield as a doublet at $\delta = 9.7$ because it couples with the methine proton (*f*).

The ring protons do not give the expected 1,4- disubstituted splitting pattern at $\delta = 7.2$ because there is insufficient difference in the environments of the protons previously labelled (d_1) and (d_2).

A small peak due to water is seen at $\delta = 1.6$. Another small peak (not seen before) appears at $\delta = 7.3$. This is from small amounts of $CHCl_3$ in the $CDCl_3$ solvent, and a similar peak is observed in the NMR spectrum of ibuprofen. It was not detected in the previous spectra because the signal from the ring protons was on top of it.

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Ibuprofen

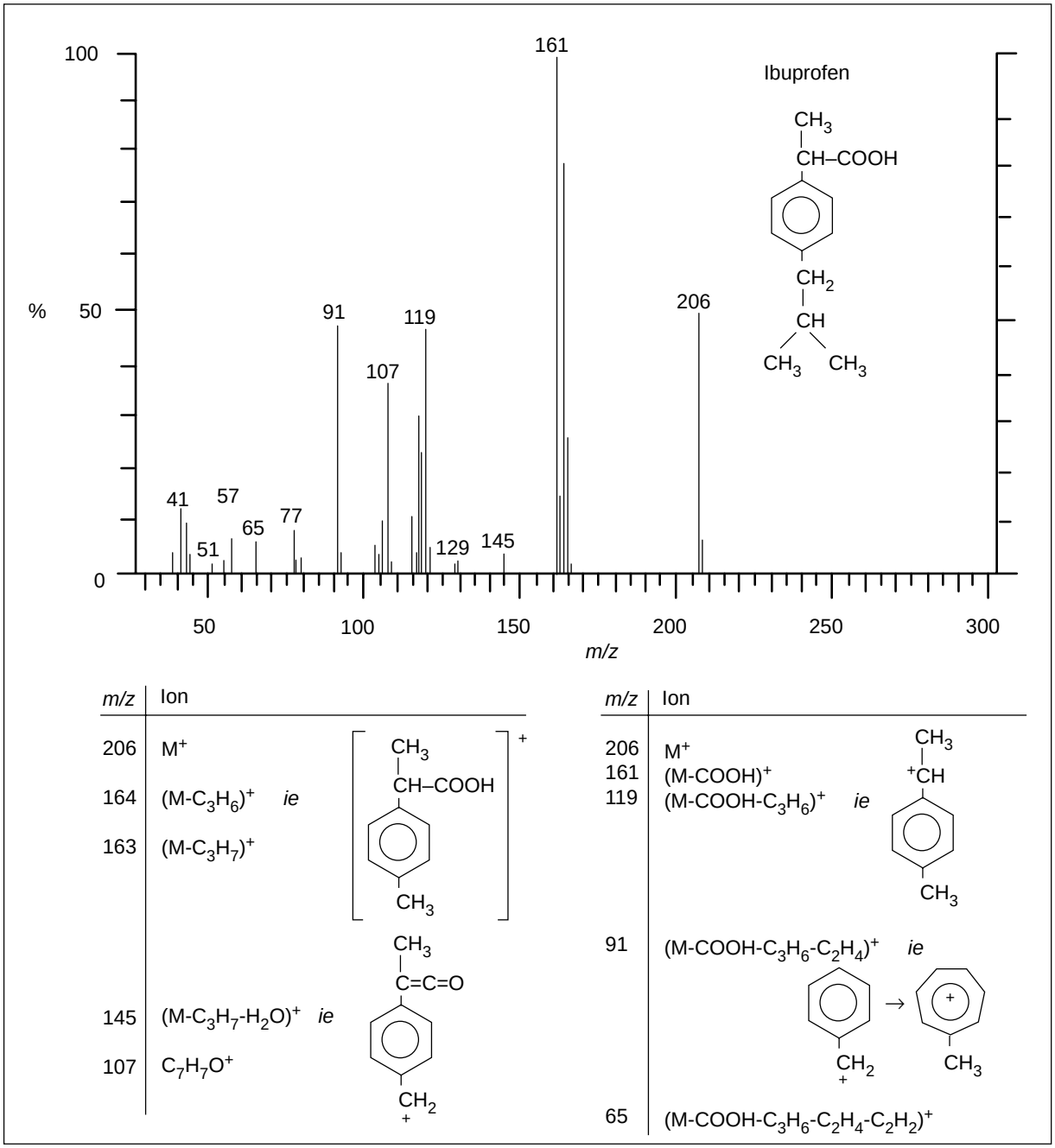

Figure 10 Mass spectrum of ibuprofen

Whereas the molecular ions of some carboxylic acids are not observed in their mass spectra because they decarboxylate when heated at low pressure (*ie* the condition of the source of the mass spectrometer) this is not the cause with Ibuprofen, as witnessed by its abundant ion at *m/z* = 206. However, it does lose water in one of its fragmentation routes. The two routes shown indicate that fragmentation occurs from both side chains, losing the carboxylic acid group is the most common first fragmentation. As with the other compounds formation of the tropyllium ion is observed.

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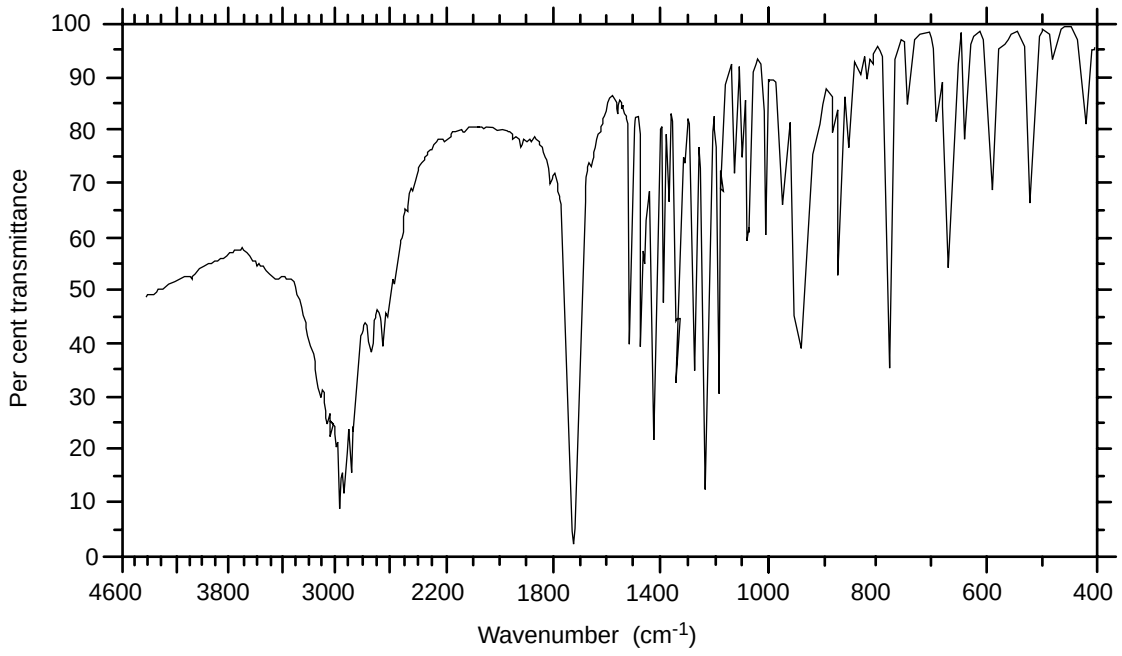

ν cm^{-1}	
3100–2800	O–H stretch of carboxylic acid dimer and water in KBr disc
2960, 2920, 2875	Aliphatic C–H stretch
2730, 2640	C–H stretch characteristic of an acid
1720	C=O stretch of aliphatic acid dimer (monomer ~1760 cm^{-1})
1510	Skeletal vibration of aromatic ring
1420	C=O bond and C–O stretch of carboxylic acid dimer
1235	C–O stretch

Ibuprofen

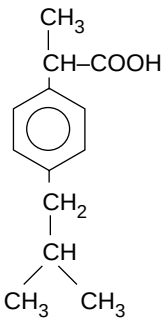

Figure 11 Infrared spectrum of ibuprofen

The high frequency end of this spectrum is dominated by the broad absorption peak of the hydrogen bonded OH group. This covers the 2500–3300 cm^{-1} range. The C–H vibrations in the 2800–3100 cm^{-1} region are still present, along with two absorptions not observed previously, characteristic of carboxylic acids at 2640 cm^{-1}and 2740 cm^{-1}respectively.

The absorption of the carbonyl group is not at the frequency expected for a carboxylic acid monomer (1760 cm^{-1}). Instead, it is observed at 1725 cm^{-1}. This is within the range expected for dimers of saturated aliphatic carboxylic acids, 1700–1725 cm^{-1}. In this case, any overtone will be lost in the signal from the edge of the OH vibration band.

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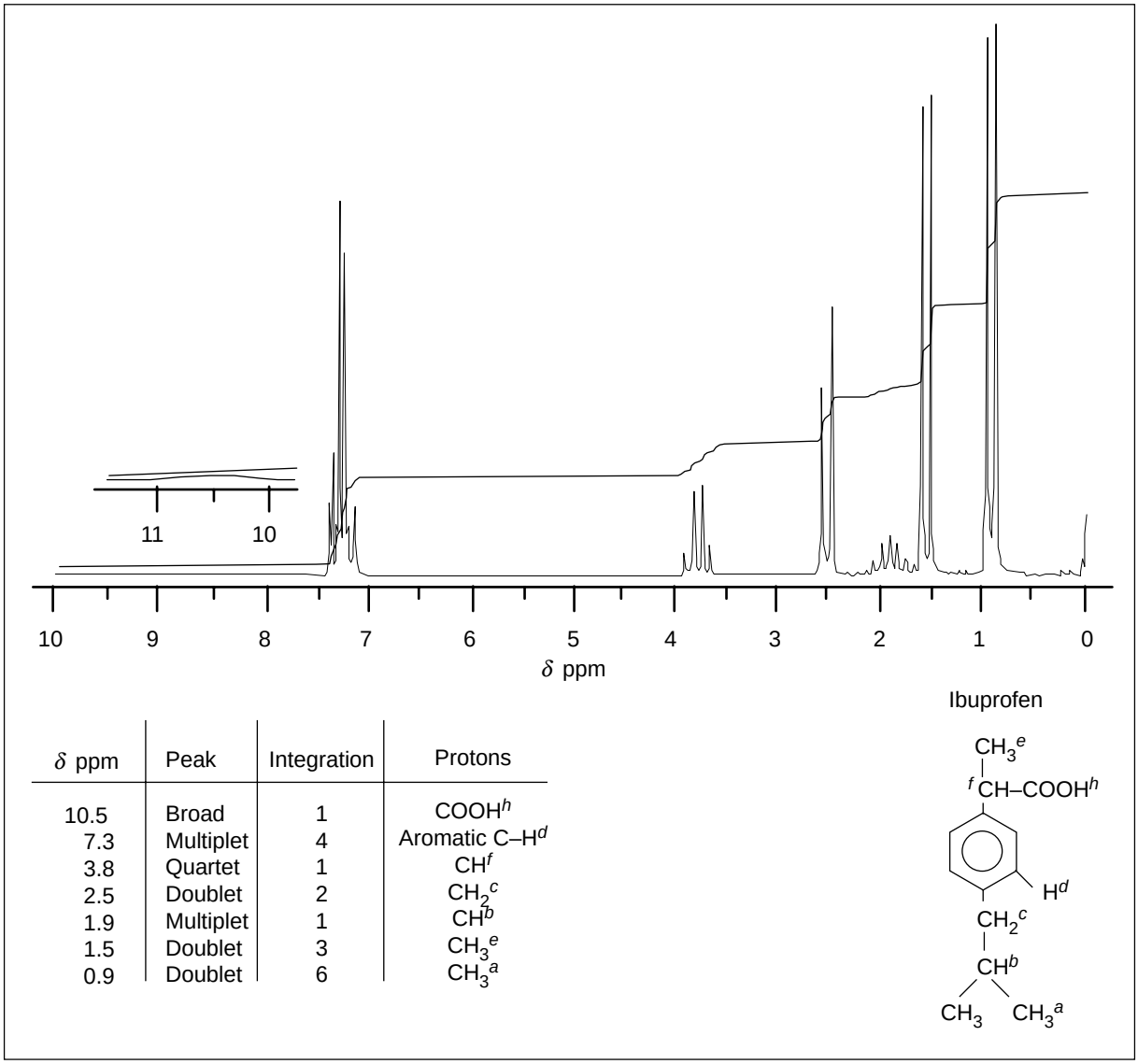

δ ppm	Peak	Integration	Protons
10.5	Broad	1	$COOH^h$
7.3	Multiplet	4	Aromatic $C–H^d$
3.8	Quartet	1	CH^f
2.5	Doublet	2	$CH_2{}^c$
1.9	Multiplet	1	CH^b
1.5	Doublet	3	$CH_3{}^e$
0.9	Doublet	6	$CH_3{}^a$

Ibuprofen

Figure 12 NMR spectrum of ibuprofen

Because the aldehyde has been oxidised, the methine proton (*f*) can couple with only the methyl protons (*e*), so its peak changes from a quartet of doublets to a simple quartet. Similarly the signal from the aldehydic proton at $\delta = 9.5$ has been lost completely. Instead, a signal is detected further downfield at $\delta = 10.5$. This is due to the acidic proton, and is not seen as a sharp peak, but a broad, weak band. This is because it exchanges rapidly with other acidic protons in the solution.

The ring protons previously labelled as d_1 and d_2 show some peak splitting because they are (again) in different electronic environments. The peak is complicated by the presence of an extra peak from the $CHCl_3$ impurity in the solvent.