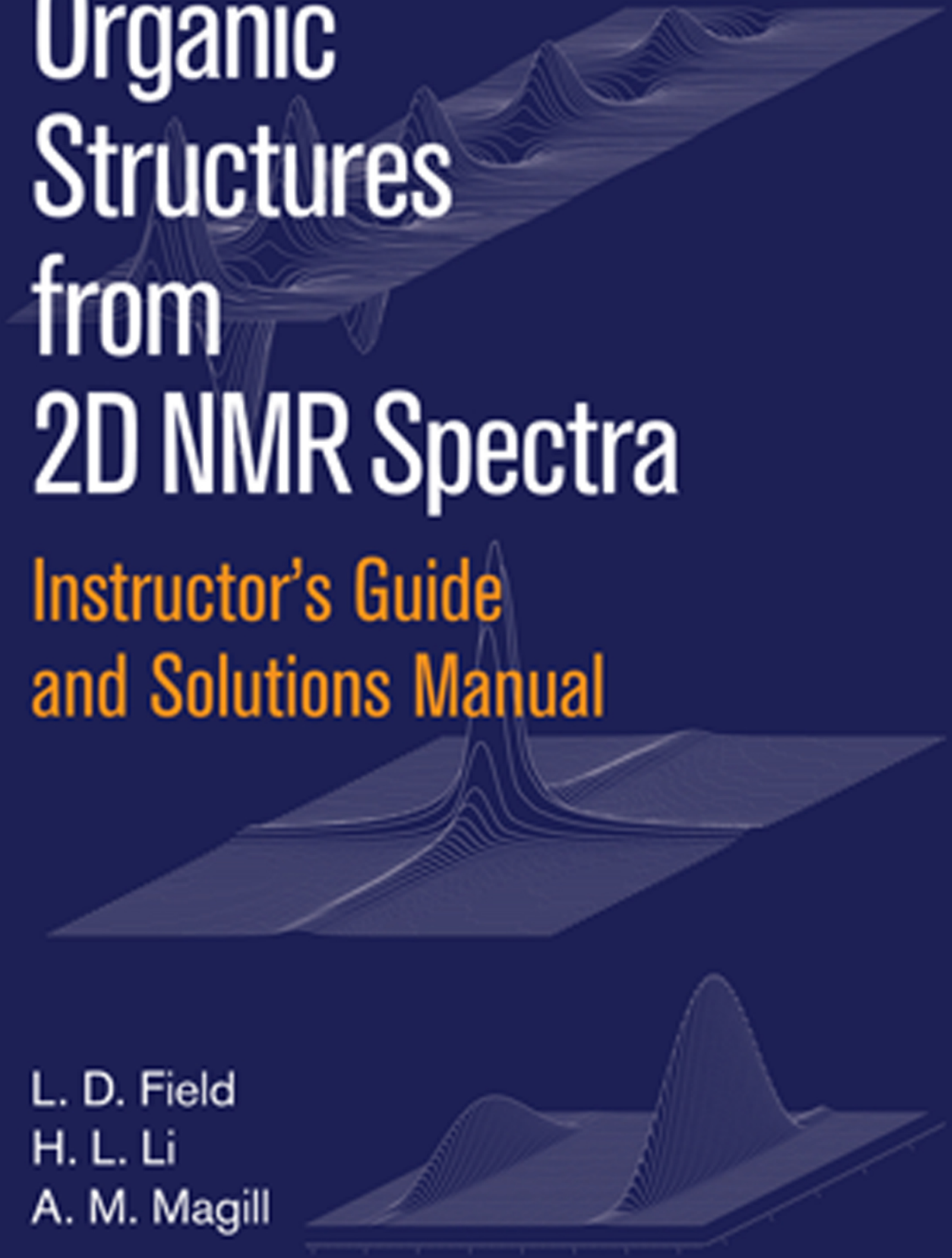
Organic Structures from 2D NMR Spectra

Instructor's Guide and Solutions Manual



L. D. Field
H. L. Li
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PREFACE

This book is the Instructor's Guide and Solutions Manual to the problems contained in the text *Organic Structures from 2D NMR Spectra*.

The aim of this book is to teach students to solve structural problems in organic chemistry using NMR spectroscopy and in particular 2D NMR spectroscopy. The basic philosophy of the book is that learning to identify organic structures using spectroscopy is best done by working through examples. This book contains a series of about 60 graded examples ranging from very elementary problems through to very challenging problems at the end of the collection.

We have assumed a working knowledge of basic structural organic chemistry and common functional groups. We also assume a working knowledge of the rudimentary spectroscopic methods which would be applied routinely in characterising and identifying organic compounds including infrared spectroscopy and basic 1D ^{13}C and ^{1}H NMR spectroscopy.

The Instructor's Guide contains a worked solution to each of the problems contained in *Organic Structures from 2D NMR Spectra*. At the outset, it should be emphasised that there are always many paths to the correct answer – there is no single process to arrive at the correct solution to any of the problems. We do not recommend a mechanical attitude to problem solving – intuition, which comes with experience, has a very important place in solving structures from spectra; however, students often find the following approach useful:

(i) **Extract as much information as possible from the basic characterisation data which is provided:**

(a) **Note the molecular formula** and any restrictions this places on the functional groups that may be contained in the molecule.

(b) From the molecular formula, **determine the degree of unsaturation**. The degree of unsaturation can be calculated from the molecular formula for all compounds containing C, H, N, O, S and the halogens using the following three basic steps:

1. Take the molecular formula and replace all halogens by hydrogens.

2. Omit all of the sulfur and/or oxygen atoms.

3. For each nitrogen, omit the nitrogen and omit one hydrogen.

After these three steps, the molecular formula is reduced to C_nH_m, and the degree of unsaturation is given by:

$$\text{Degree of Unsaturation} = n - {}^{m}/_{2} + 1$$

The degree of unsaturation indicates the number of π bonds and/or rings that the compound contains. For example, if the degree of unsaturation is 1, the molecule can only contain one double bond or one ring. If the degree of unsaturation is 4, the molecule must contain four rings or multiple bonds. An aromatic ring accounts for four degrees of unsaturation (the equivalent of three double bonds and a ring). An alkyne or a C≡N accounts for two degrees of unsaturation (the equivalent of two π bonds).

(c) **Analyse the 1D ^{1}H NMR spectrum** if one is provided and note the relative numbers of protons in different environments and any obvious information contained in the coupling patterns. Note the presence of aromatic protons, exchangeable protons, and/or vinylic protons, all of which provide valuable information on the functional groups which may be present.

(d) **Analyse the 1D ^{13}C NMR spectrum** if one is provided and note the number of carbons in different environments. Note also any resonances that would be characteristic of specific functional groups, *e.g.* the presence or absence of a ketone, aldehyde, ester or carboxylic acid carbonyl resonance.

(e) **Analyse any infrared data** and note whether there are absorptions characteristic of specific functional groups, *e.g.* C=O or –OH groups.

(ii) **Extract basic information from the 2D COSY, TOCSY and/or C–H correlation spectra**.

(a) The COSY will provide obvious coupling partners. If there is one identifiable starting point in a spin system, the COSY will allow the successive identification (*i.e.* the sequence) of all nuclei in the spin system. The COSY cannot jump across breaks in the spin system (such as where there is a heteroatom or a carbonyl group that isolates one spin system from another).

(b) The TOCSY identifies all groups of protons that are in the same spin system.

(c) The C–H correlation links the carbon signals with their attached protons and also identifies how many –CH–, $–CH_2–$, $–CH_3$ and quaternary carbons are in the molecule.

(iii) **Analyse the INADEQUATE spectrum** if one is provided, because this can sequentially provide the whole carbon skeleton of the molecule. Choose one signal as a starting point and sequentially work through the INADEQUATE spectrum to determine which carbons are connected to which.

(iv) **Analyse the HMBC spectrum.** This is perhaps the most useful technique to pull together all of the fragments of a molecule because it gives long-range connectivity.

(v) **Analyse the NOESY spectrum** to assign any stereochemistry in the structure.

(vi) **Continually update the list of structural elements** or fragments that have been conclusively identified at each step and start to pull together reasonable possible structures. Be careful not to jump to possible solutions before the evidence is conclusive. Keep assessing and re-assessing all of the options.

(vii) When you have a final solution which you believe is correct, **go back and confirm that all of the spectroscopic data are consistent with the final structure** and that every peak in every spectrum can be properly rationalised in terms of the structure that you have proposed.

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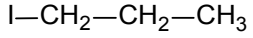
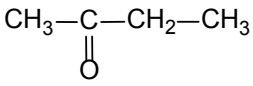
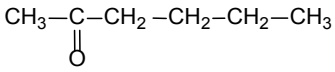
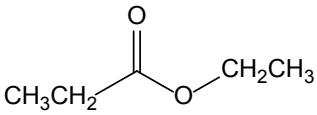
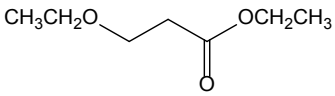
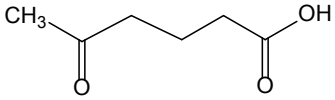
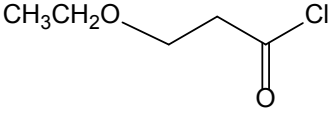
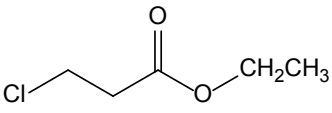
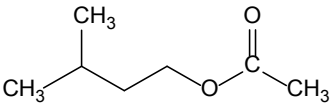
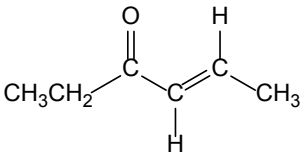
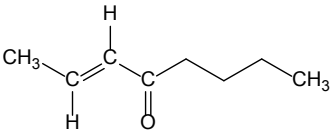
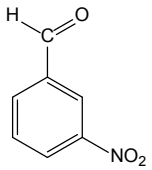
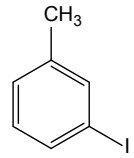
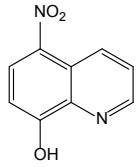
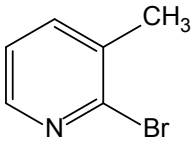
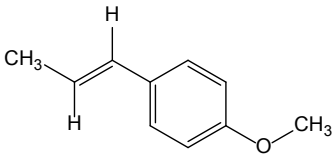
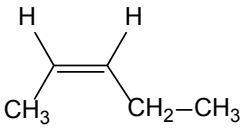
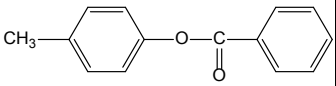
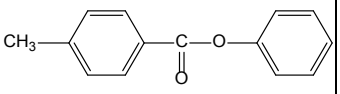
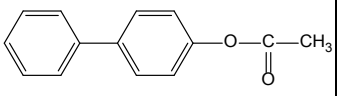
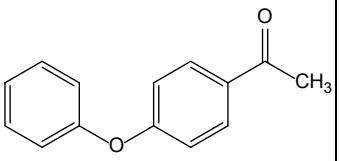
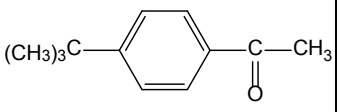
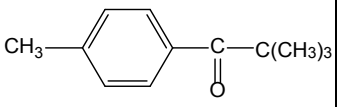
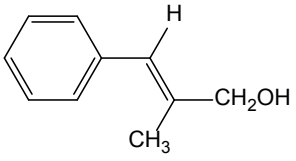
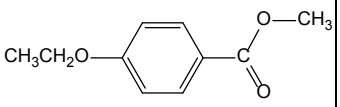
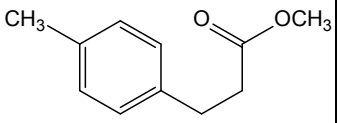
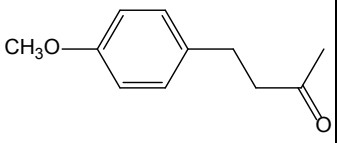
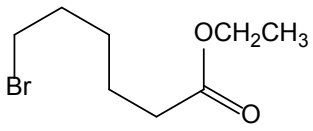
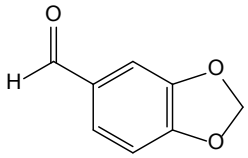
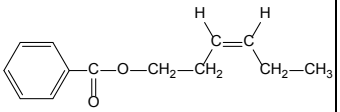
January 2015

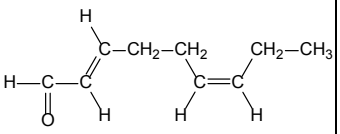
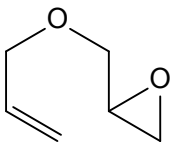
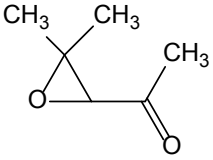
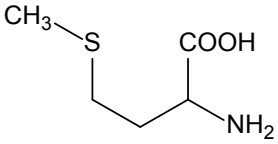
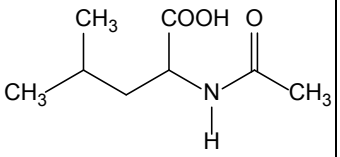
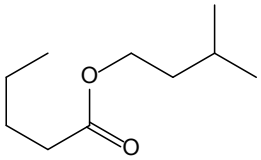
1	 1-iodopropane C_3H_7I	LABEL COSY HSQC HMBC INADEQUATE
2	 2-butanone C_4H_8O	LABEL COSY HSQC HMBC INADEQUATE
3	 2-hexanone $C_6H_{12}O$	COSY HSQC HMBC
4	 ethyl propionate $C_5H_{10}O_2$	SIMULATE COSY HSQC HMBC
5	 ethyl 3-ethoxypropionate $C_7H_{14}O_3$	LABEL COSY HSQC HMBC
6	 4-acetylbutyric acid $C_6H_{10}O_3$	ASSIGNMENT HSQC HMBC
7	 3-ethoxypropionyl chloride $C_5H_9ClO_2$	COSY HSQC HMBC ISOMER (2)
8	 ethyl 3-chloropropionate $C_5H_9ClO_2$	COSY HSQC HMBC ISOMER (2)
9	 isoamyl acetate $C_7H_{14}O_2$	LABEL COSY HSQC HMBC INADEQUATE
10	 *trans*-4-hexen-3-one $C_6H_{10}O$	LABEL COSY HSQC HMBC NOESY
11	 *trans*-2-octen-4-one $C_8H_{14}O$	COSY HSQC HMBC NOESY
12	 3-nitrobenzaldehyde $C_7H_5NO_3$	LABEL COSY HSQC HMBC NOESY INADEQUATE

Organic Structures from 2D NMR Spectra

13  3-iodotoluene C_7H_6I	SIMULATE HSQC HMBC
14  8-hydroxy-5-nitroquinoline $C_9H_6N_2O_3$	LABEL COSY HSQC HMBC INADEQUATE
15  2-bromo-3-picoline C_6H_6BrN	HSQC HMBC
16  *trans*-anethole $C_{10}H_{12}O$	SIMULATE COSY NOESY
17  *cis*-2-pentene C_5H_{10}	COSY HSQC NOESY
18  *p*-tolyl benzoate $C_{14}H_{12}O_2$	COSY HSQC HMBC ISOMER (4)

19  phenyl *p*-toluate $C_{14}H_{12}O_2$	COSY HSQC HMBC ISOMER (4)
20  4-biphenylyl acetate $C_{14}H_{12}O_2$	COSY HSQC HMBC ISOMER (4)
21  4'-phenoxyacetophenone $C_{14}H_{12}O_2$	COSY HSQC HMBC ISOMER (4)
22  4'-*tert*-butylacetophenone $C_{12}H_{16}O$	HSQC HMBC ISOMER (2)
23  2,2,4'-trimethyl-propiophenone $C_{12}H_{16}O$	HSQC HMBC ISOMER (2)
24  *trans*-2-methyl-3-phenyl-2-propen-1-ol $C_{10}H_{12}O$	COSY HSQC HMBC NOESY

25  methyl 4-ethoxybenzoate $C_{10}H_{12}O_3$	COSY HSQC HMBC
26  methyl 3-(*p*-tolyl)propionate $C_{11}H_{14}O_2$	COSY HSQC HMBC ISOMER (2)
27  4-(4'-methoxyphenyl)-2-butanone $C_{11}H_{14}O_2$	HSQC INADEQUATE ISOMER (2)
28  ethyl 6-bromohexanoate $C_8H_{15}BrO_2$	ASSIGNMENT COSY HSQC
29  piperonal $C_8H_6O_3$	SIMULATE HSQC HMBC
30  *cis*-3-hexenyl benzoate $C_{13}H_{16}O_2$	COSY HSQC HMBC NOESY

31  *trans*-2,*cis*-6-nonadienal $C_9H_{14}O$	COSY HSQC HMBC NOESY
32  allyl glycidyl ether $C_6H_{10}O_2$	COSY HSQC HMBC ISOMER (2)
33  3,4-epoxy-4-methyl-2-pentanone $C_6H_{10}O_2$	HSQC HMBC ISOMER (2)
34  *dl*-methionine $C_5H_{11}NO_2S$	IDENTIFY 1 HSQC HMBC
35  *N*-acetyl-*l*-leucine $C_8H_{15}NO_3$	COSY HSQC HMBC
36  isoamyl valerate $C_{10}H_{20}O_2$	TOCSY HSQC

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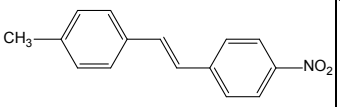
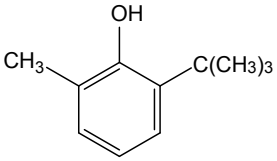
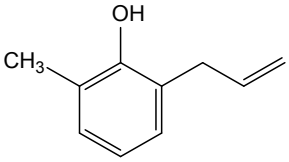
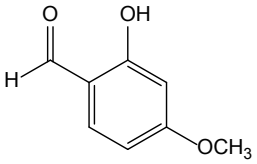
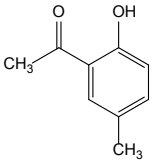
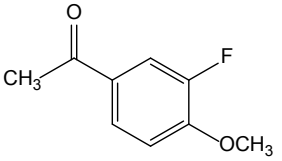
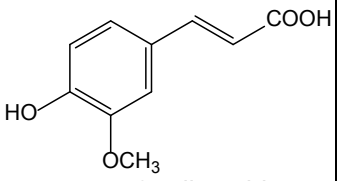
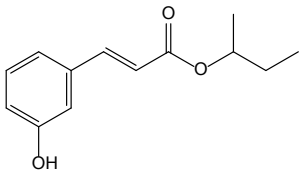
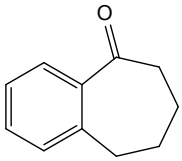
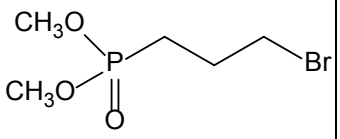
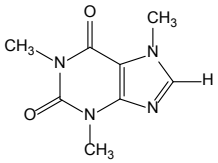
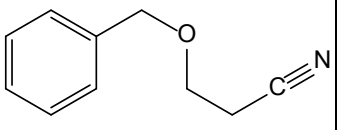
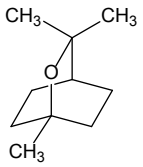
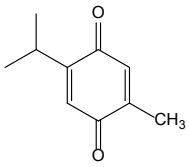
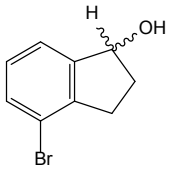
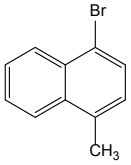
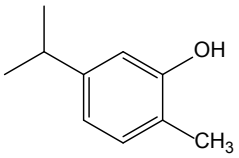
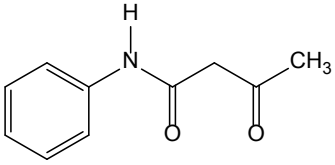
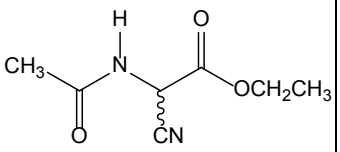
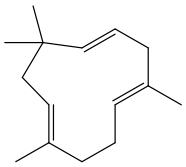
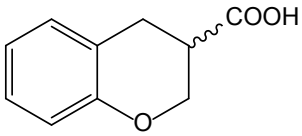
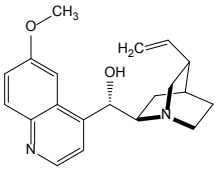
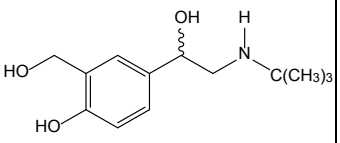
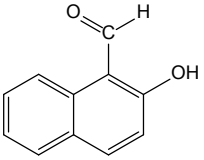
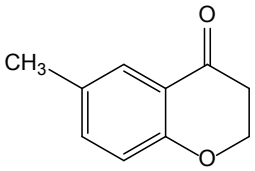
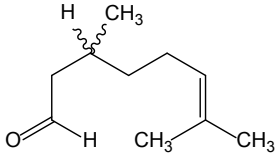
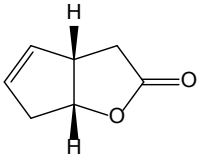
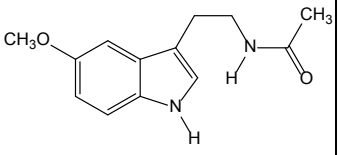
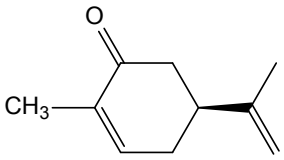
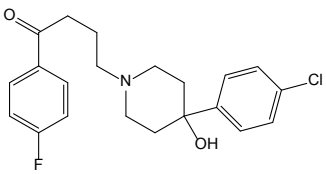
37  *(E)*-4-methyl-4'-nitrostilbene $C_{15}H_{13}NO_2$	ASSIGNMENT COSY HSQC HMBC
38  2-*tert*-butyl-6-methylphenol $C_{11}H_{16}O$	HSQC HMBC
39  2-allyl-6-methylphenol $C_{10}H_{12}O$	COSY HSQC HMBC
40  2-hydroxy-4-methoxy-benzaldehyde $C_8H_8O_3$	HSQC HMBC
41  2'-hydroxy-5'-methylacetophenone $C_9H_{10}O_2$	HSQC HMBC
42  3'-fluoro-4'-methoxyacetophenone $C_9H_9FO_2$	HSQC NOESY HETEROATOM
43  *trans*-ferulic Acid $C_{10}H_{10}O_4$	COSY HSQC HMBC
44  *seC*–butyl 3-hydroxycinnamate $C_{13}H_{16}O_3$	COSY HSQC HMBC
45  1-benzosuberone $C_{11}H_{12}O$	ASSIGNMENT COSY HSQC HMBC
46  dimethyl (3-bromo-propyl)phosphonate $C_5H_{12}BrO_3P$	COSY HSQC P-H HMBC HETEROATOM
47  caffeine $C_8H_{10}N_4O_2$	ASSIGNMENT HSQC HMBC N-H HSQC HETEROATOM
48  benzyloxypropionitrile $C_{10}H_{11}NO$	COSY HSQC HMBC

49	 cineole $C_{10}H_{18}O$	HSQC INADEQUATE
50	 thymoquinone $C_{10}H_{12}O_2$	IDENTIFY 1 HSQC HMBC
51	 4-bromo-1-indanol C_9H_9BrO	COSY HSQC HMBC
52	 1-bromo-4-methylnaphthalene $C_{11}H_9Br$	ASSIGNMENT COSY HSQC HMBC
53	 carvacrol $C_{10}H_{14}O$	COSY HSQC HMBC
54	 acetoacetanilide $C_{10}H_{11}NO_2$	HSQC HMBC NOESY
55	 ethyl acetamido-cyanoacetate $C_7H_{10}N_2O_3$	COSY HSQC HMBC N-H HSQC N-H HMBC
56	 α-Humulene $C_{15}H_{24}$	HSQC INADEQUATE
57	 3,4-dihydro-2*H*–benzo-pyran-3-carboxylic acid $C_{10}H_{10}O_3$	COSY HSQC HMBC
58	 quinidine $C_{20}H_{24}N_2O_2$	ASSIGNMENT COSY HSQC HMBC NOESY
59	 salbutamol $C_{13}H_{21}NO_3$	COSY HSQC HMBC NOESY N-H HMBC HETEROATOM
60	 2-hydroxy-1-naphthaldehyde $C_{11}H_8O_2$	COSY HSQC HMBC

Organic Structures from 2D NMR Spectra

61  6-methyl-4-chromanone $C_{10}H_{10}O_2$	HSQC HMBC INADEQUATE
62  citronellal $C_{10}H_{18}O$	COSY HSQC HMBC
63  (+)-*cis*-2-oxabicyclo-[3.3.0]oct-6-en-3-one $C_7H_8O_2$	COSY HSQC HMBC NOESY

64  melatonin $C_{13}H_{16}N_2O_2$	COSY HSQC HMBC NOESY N-H HSQC N-H HMBC HETEROATOM
65  carvone $C_{10}H_{14}O$	COSY HSQC HMBC
66  haloperidol $C_{21}H_{23}ClFNO_2$	ASSIGNMENT COSY HSQC HMBC HETEROATOM

Problem 1

Question:

The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of 1-iodopropane (C_3H_7I) recorded in $CDCl_3$ solution at 298 K and 400 MHz are given below.

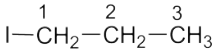
The ^{1}H NMR spectrum has signals at δ 0.99 (H_3), 1.84 (H_2) and 3.18 (H_1) ppm.

The $^{13}C\{^{1}H\}$ NMR spectrum has signals at δ 9.6 (C_1), 15.3 (C_3) and 26.9 (C_2) ppm.

Also given on the following pages are the ^{1}H–^{1}H COSY, ^{1}H–^{13}C me-HSQC, ^{1}H–^{13}C HMBC and INADEQUATE spectra. For each 2D spectrum, indicate which correlation gives rise to each cross-peak by placing an appropriate label in the box provided (*e.g.* $H_1 \rightarrow H_2$, $H_1 \rightarrow C_1$).

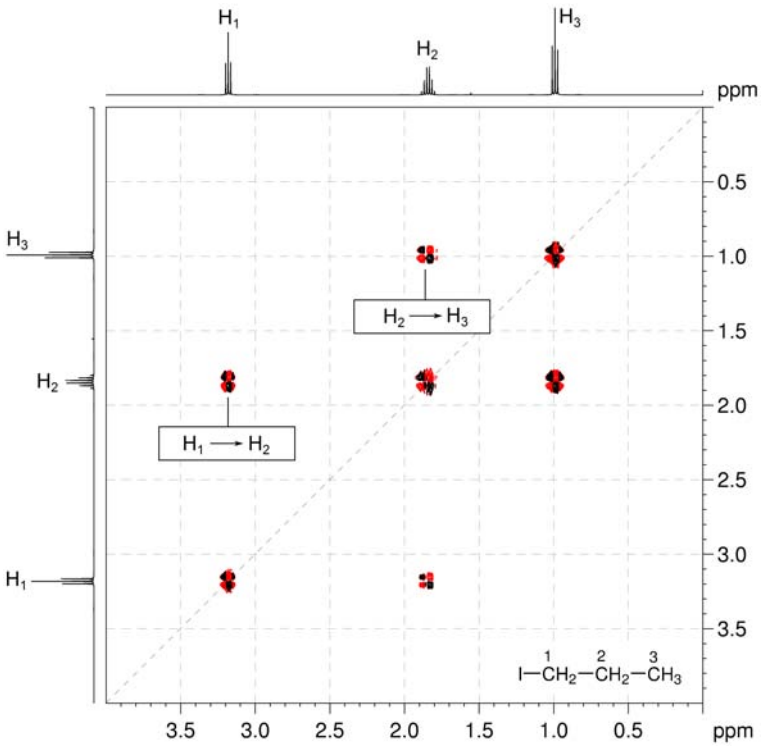
Solution:

1-Iodopropane



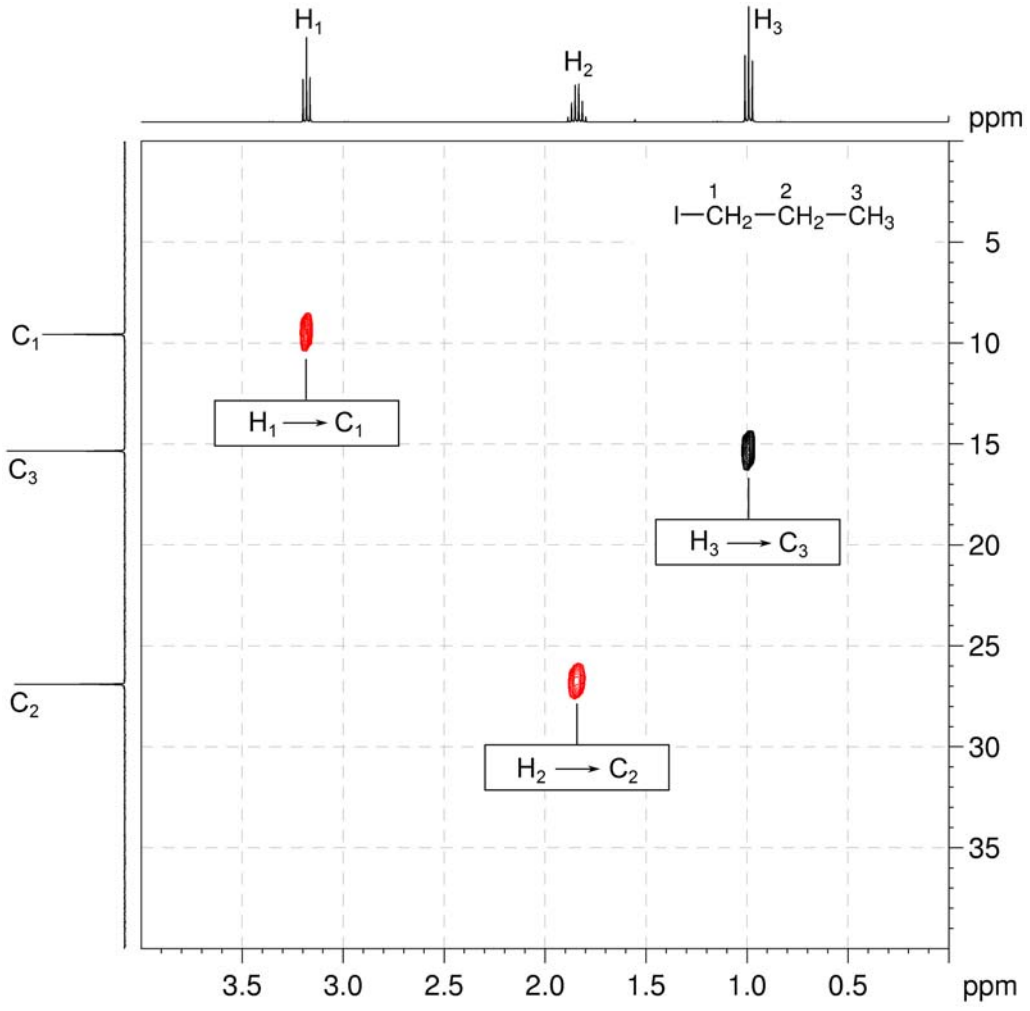
1. ^{1}H–^{1}H COSY spectra show which pairs of protons are coupled to each other. The COSY spectrum is always symmetrical about a diagonal. In the COSY spectrum, there are two $^{3}J_{H-H}$ correlations above the diagonal ($H_1 \rightarrow H_2$ and $H_2 \rightarrow H_3$). There are no long-range correlations.

^{1}H–^{1}H COSY spectrum of 1-iodopropane ($CDCl_3$, 400 MHz)



2. The ^{1}H–^{13}C me-HSQC spectrum shows direct (one-bond) correlations between proton and carbon nuclei, so there will be cross-peaks between H_1 and C_1, H_2 and C_2 and also between H_3 and C_3. As the spectrum is multiplicity edited, the cross-peaks corresponding to CH_2 groups are shown in red and are of opposite phase to those for CH_3 groups.

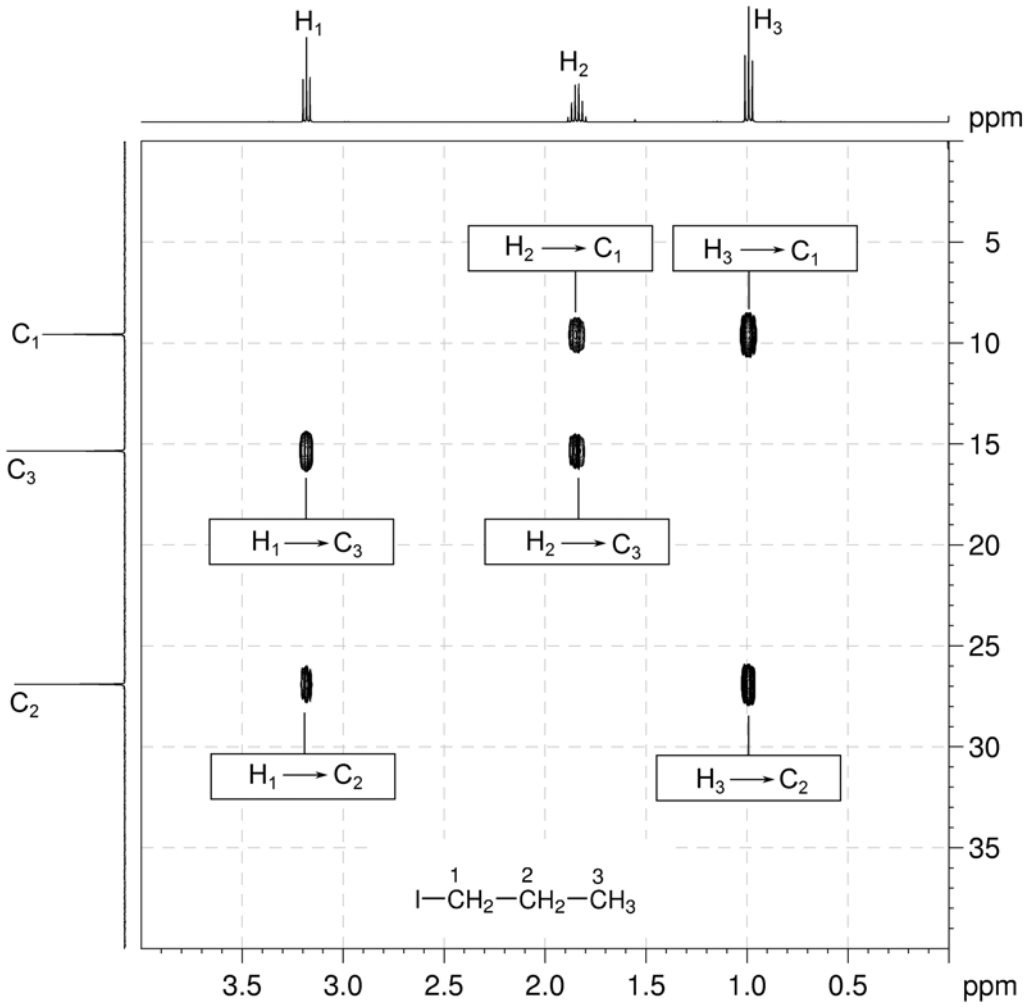
^{1}H–^{13}C me-HSQC spectrum of 1-iodopropane ($CDCl_3$, 400 MHz)



3. In HMBC spectra, remember that, for alkyl systems, both two- and three-bond C–H coupling can give rise to strong cross-peaks.

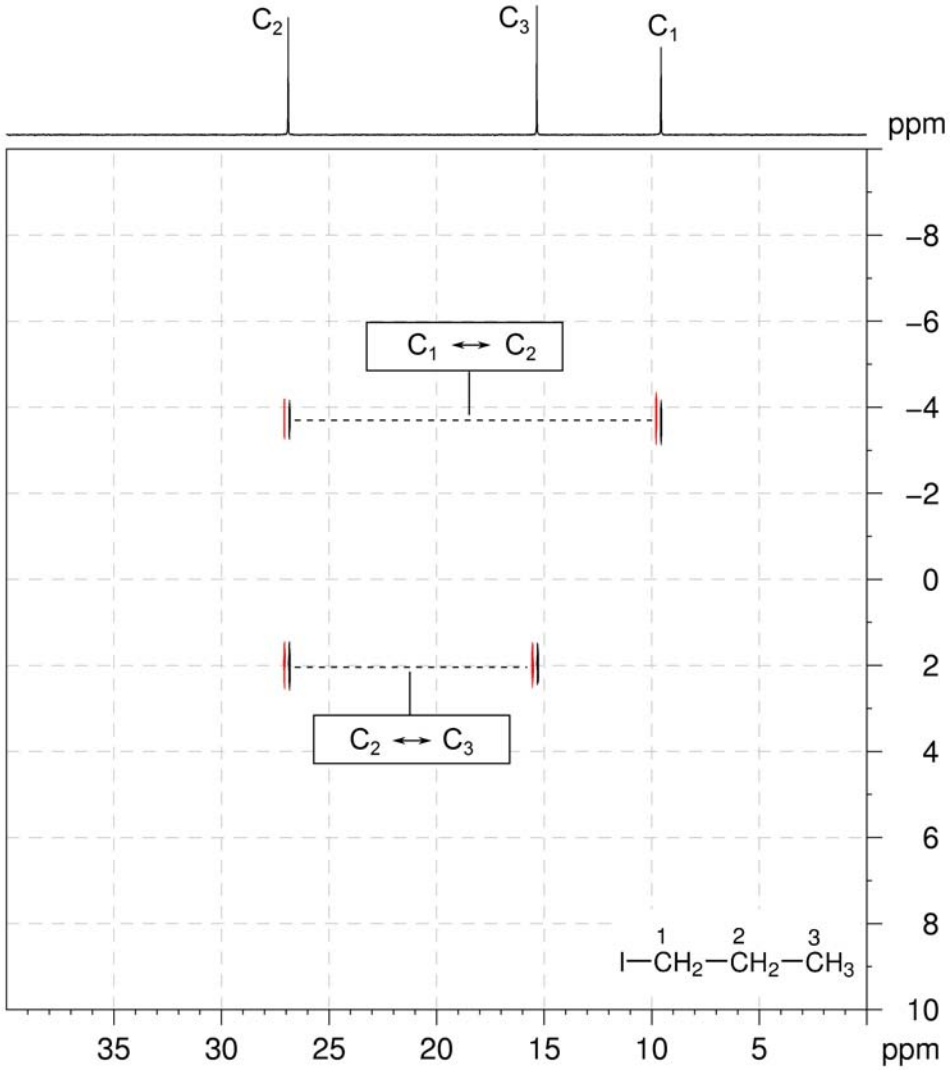
4. H_1 correlates to C_2 and C_3. H_2 correlates to C_1 and C_3. H_3 correlates to C_1 and C_2.

^{1}H–^{13}C HMBC spectrum of 1-iodopropane ($CDCl_3$, 400 MHz)



5. The INADEQUATE spectrum shows one-bond ^{13}C–^{13}C connectivity. There are correlations between C_1 and C_2, and C_2 and C_3.

INADEQUATE spectrum of 1-iodopropane ($CDCl_3$, 150 MHz)



Problem 2

Question:

The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of 2-butanone (C_4H_8O) recorded in $CDCl_3$ solution at 298 K and 400 MHz are given below.

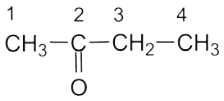
The ^{1}H NMR spectrum has signals at δ 1.05 (H_4), 2.14 (H_1) and 2.47 (H_3) ppm.

The $^{13}C\{^{1}H\}$ NMR spectrum has signals at δ 7.2 (C_4), 28.8 (C_1), 36.2 (C_3) and 208.8 (C_2) ppm.

Also given on the following pages are the ^{1}H–^{1}H COSY, ^{1}H–^{13}C me-HSQC, ^{1}H–^{13}C HMBC and INADEQUATE spectra. For each 2D spectrum, indicate which correlation gives rise to each cross-peak by placing an appropriate label in the box provided (*e.g.* $H_1 \rightarrow H_2$, $H_1 \rightarrow C_1$).

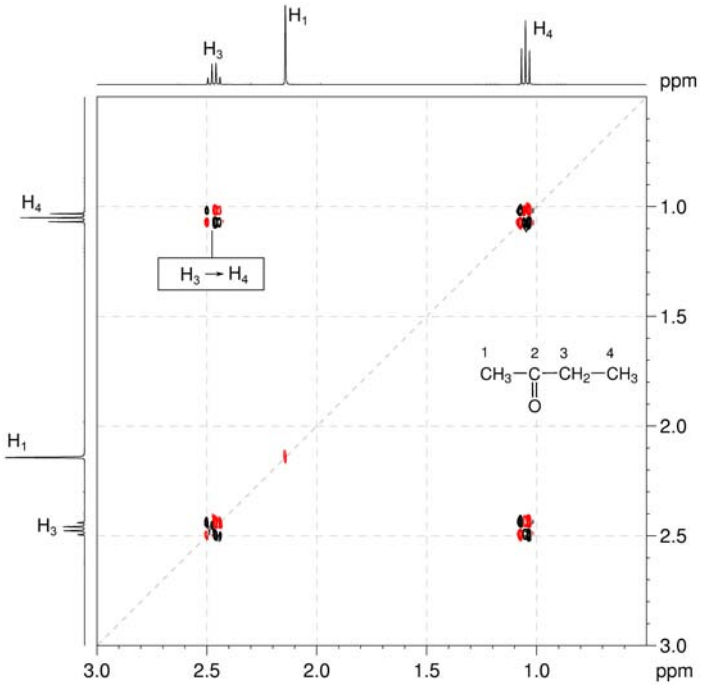
Solution:

2-Butanone



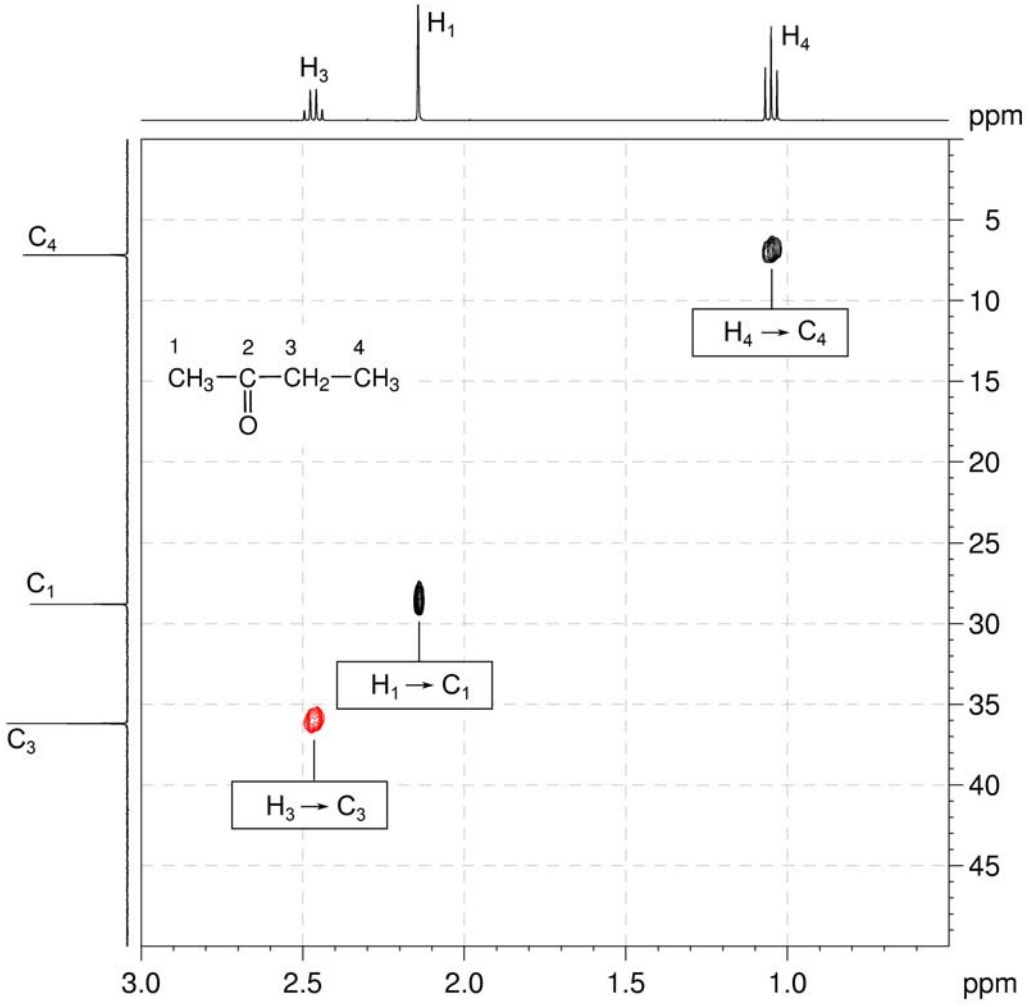
1. ^{1}H–^{1}H COSY spectra show which pairs of protons are coupled to each other. The COSY spectrum is always symmetrical about a diagonal. In the COSY spectrum, there is only one $^{3}J_{H-H}$ correlation above the diagonal ($H_3 \rightarrow H_4$). There are no long-range correlations.

^{1}H–^{1}H COSY spectrum of 2-butanone ($CDCl_3$, 400 MHz)



2. The $^{1}H–^{13}C$ me-HSQC spectrum shows direct (one-bond) correlations between proton and carbon nuclei, so there will be cross-peaks between H_1 and C_1, H_3 and also between C_3 and H_4 and C_4. As the spectrum is multiplicity edited, the cross-peaks corresponding to CH_2 groups are shown in red and are of opposite phase to those for CH_3 groups.

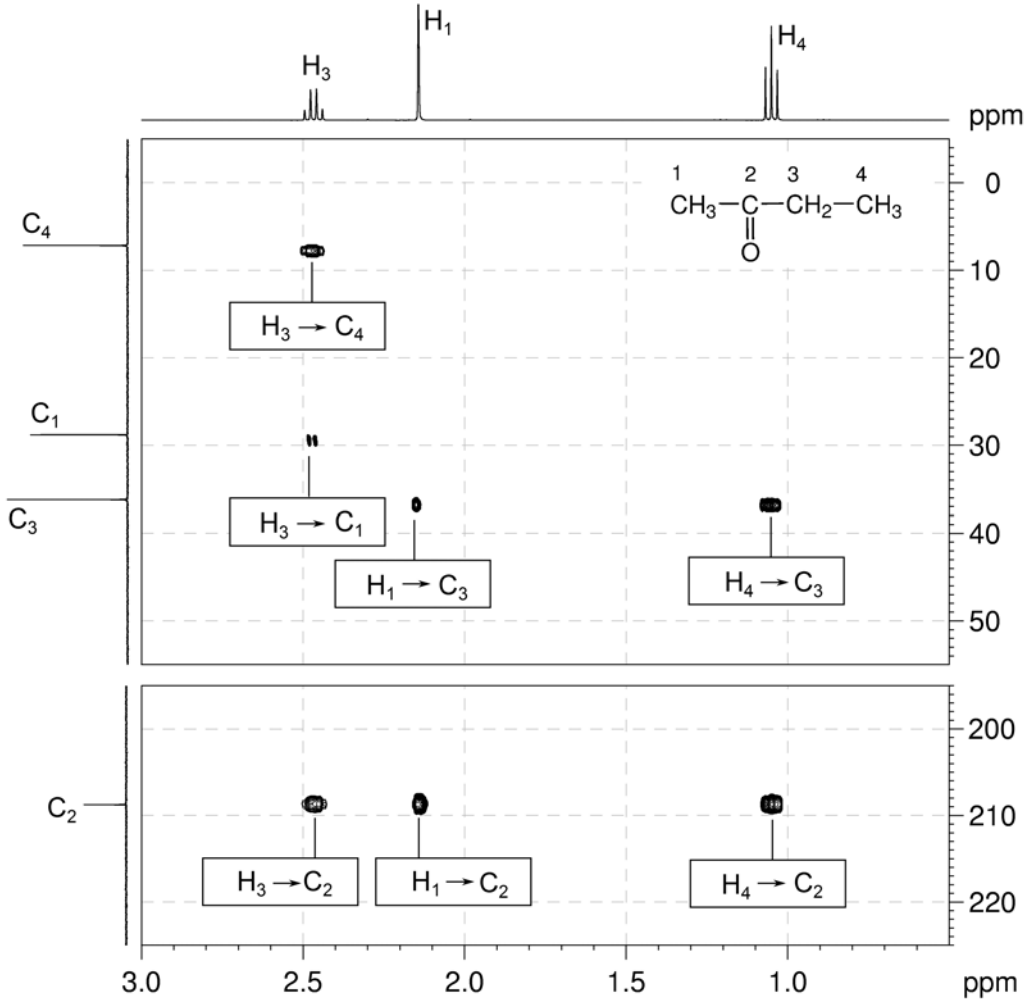
$^{1}H–^{13}C$ me-HSQC spectrum of 2-butanone ($CDCl_3$, 400 MHz)



3. In HMBC spectra, remember that, for alkyl systems, both two- and three-bond coupling can give rise to strong cross-peaks. There are no one-bond C–H correlations.

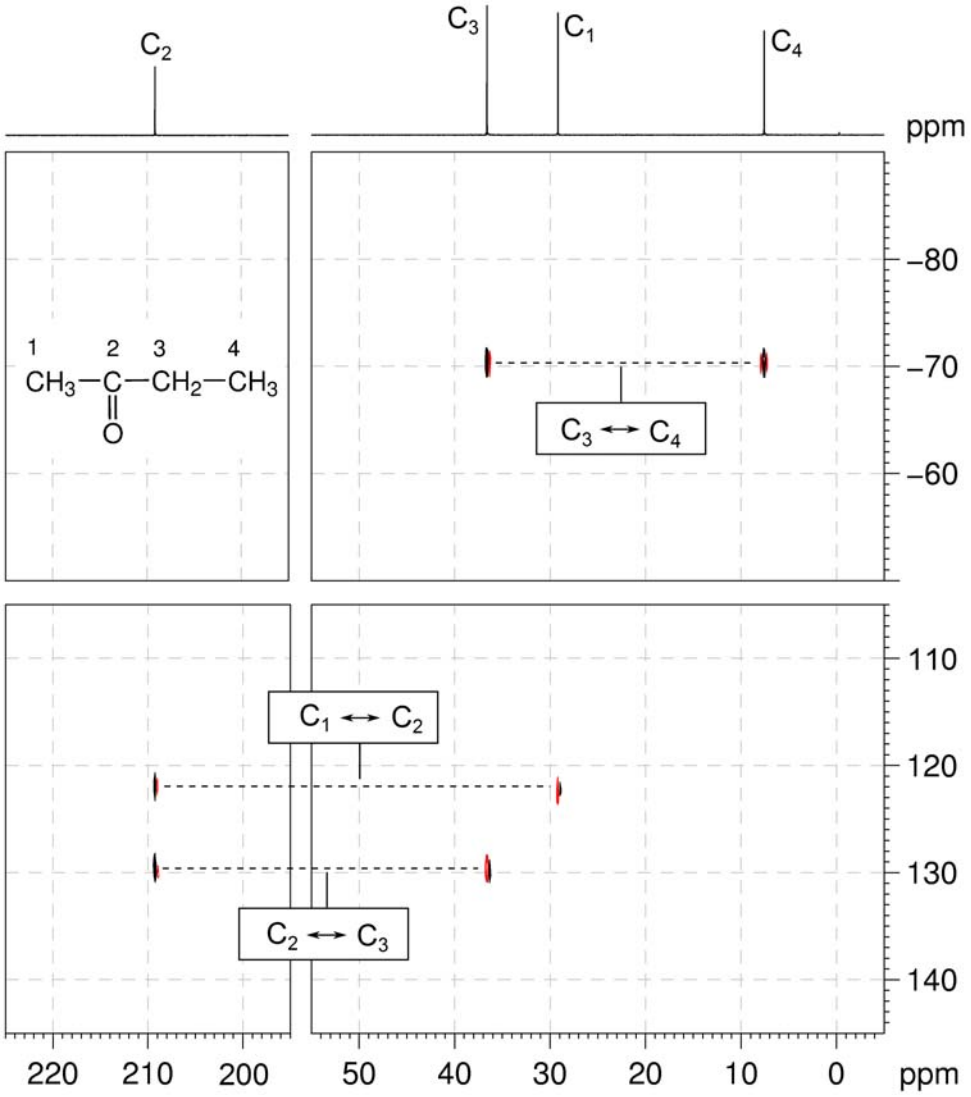
4. H_1 correlates to C_2 and C_3. H_3 correlates to C_1, C_2 and C_4. H_4 correlates to C_2 and C_3.

^{1}H–^{13}C HMBC spectrum of 2-butanone ($CDCl_3$, 400 MHz)



5. The INADEQUATE spectrum shows one-bond ^{13}C–^{13}C connectivity. There are correlations between C_1 and C_2, C_2 and C_3 and C_3 and C_4.

INADEQUATE spectrum of 2-butanone ($CDCl_3$, 150 MHz)



Problem 3

Question:

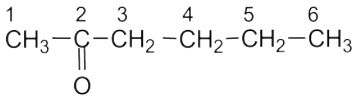
Identify the following compound.

Molecular Formula: $C_6H_{12}O$

IR: 1718 cm^{-1}

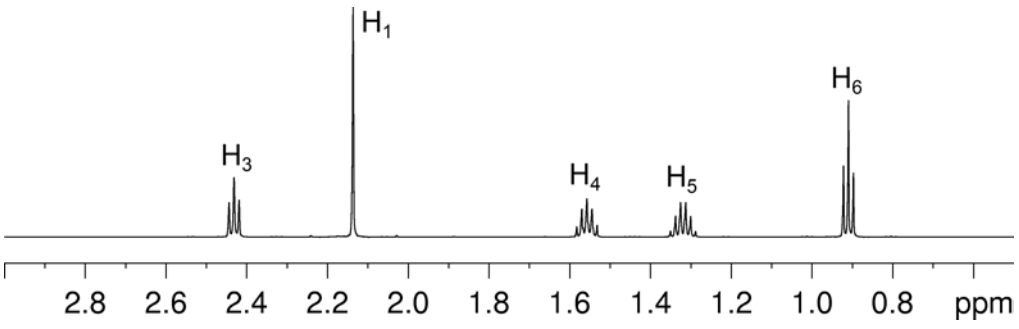
Solution:

2-Hexanone

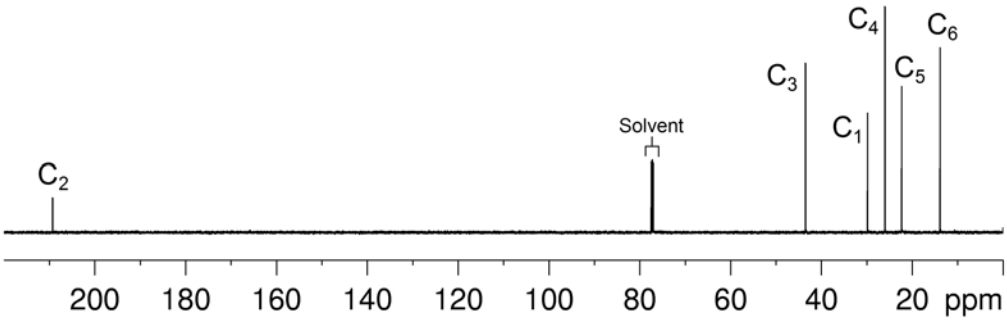


1. The molecular formula is $C_6H_{12}O$. Calculate the degree of unsaturation from the molecular formula: ignore the O atom to give an effective molecular formula of C_6H_{12} (C_nH_m) which gives the degree of unsaturation as $(n - m/2 + 1) = 6 - 6 + 1 = 1$. The compound contains one ring or one functional group containing a double bond.
2. The $^{13}C\{^1H\}$ spectrum establishes that the compound contains a ketone (^{13}C resonance at 209.3 ppm). There can be no other double bonds or rings in the molecule because the C=O accounts for the single degree of unsaturation.
3. 1D NMR spectra establish the presence of three CH_2 groups and two CH_3 groups. The multiplicities of the signals can be verified using the me-HSQC spectrum.

^1H NMR spectrum of 2-hexanone ($CDCl_3$, 600 MHz)



$^{13}C\{H\}$ NMR spectrum of 2-hexanone ($CDCl_3$, 150 MHz)



4. The COSY spectrum shows a single spin system – $H_3 \rightarrow H_4$, $H_4 \rightarrow H_5$ and $H_5 \rightarrow H_6$ for a $–CH_2CH_2CH_2CH_3$ fragment.

5. H_1 does not couple to any of the other protons in the molecule and therefore does not show any correlations in the COSY spectrum.

$^1H–^1H$ COSY spectrum of 2-hexanone ($CDCl_3$, 600 MHz)