

Determination of stereochemistry by spectroscopic methods

32

Connections

Building on:

- Determining organic structures [ch3](#)
- Proton NMR spectroscopy [ch11](#)
- Review of spectroscopic methods [ch15](#)
- Stereochemistry [ch16](#)
- Conformation [ch18](#)
- Controlling double bond geometry [ch31](#)

Arriving at:

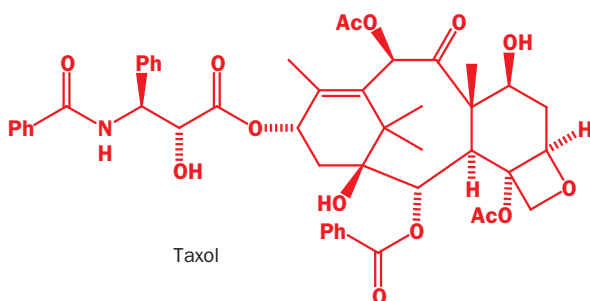
- How coupling varies with the angle between bonds
- How ring size affects coupling
- How electronegative atoms reduce coupling
- How π systems increase geminal coupling
- How protons attached to the same carbon can be different, and can couple to one another
- What homotopic, enantiotopic, and diastereotopic mean
- The nuclear Overhauser effect: what it is and how to exploit it

Looking forward to:

- Controlling stereochemistry with rings [ch33](#)
- Diastereoselectivity [ch34](#)
- Saturated heterocycles [ch42](#)
- Asymmetric synthesis [ch45](#)
- Organic synthesis [ch 53](#)

Introduction

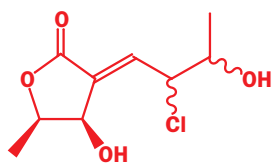
From time to time throughout the book we have spread before your eyes some wonderful structures. Some have been very large and complicated (such as palytoxin, p. 19) and some small but difficult to believe (such as tetra-*t*-butyl tetrahedrane, p. 373). They all have one thing in common. Their structures were determined by spectroscopic methods and everyone believes them to be true. Among the most important organic molecules today is Taxol, an anticancer compound from yew trees. Though it is a ‘modern’ compound, in that chemists became interested in it only in the 1990s, its structure was actually determined in 1971.



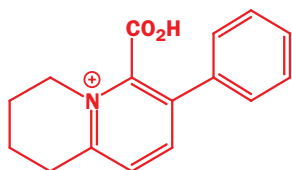
No one argued with this structure because it was determined by reliable spectroscopic methods—NMR plus an X-ray crystal structure of a derivative. This was not always the case. Go back another 25 years to 1946 and chemists argued about structures all the time. An undergraduate and an NMR spectrometer can solve in a few minutes structural problems that challenged teams of chemists for years half a century ago. In this chapter we will combine the knowledge presented systematically in Chapters 3, 11, and 15, add your more recently acquired knowledge of stereochemistry (Chapters 16, 18, and 31), and show you how structures are actually determined in all their stereochemical detail using all the evidence available.

In general, we will not look at structures as complex as Taxol. But it is worth a glance at this stage to see what was needed. The basic carbon skeleton contains one eight- and two six-membered rings. These can be deduced from proton and carbon NMR. There is a four-membered heterocyclic ring—a feature that caused a lot of argument over the structure of penicillin. The four-membered cyclic ether in Taxol is easily deduced from proton NMR as we will see soon. There are ten functional groups (at least—it depends on how you count) including six carbonyl groups. These are easily seen in the carbon NMR and IR spectra. Finally, there is the stereochemistry. There are eleven stereogenic centres, which were deduced mostly from the proton NMR and the X-ray crystal structure of a closely related compound (Taxol itself is not crystalline).

two recently discovered simple natural products



chlorocarolide A



clathrymine A

It would be wise to review Chapter 18 now if what we said there is not fresh in your mind.

New structures are being determined all the time. A recent issue of one important journal (*Tetrahedron Letters* No. 14 of 1996) has a paper on Taxol but also reports the discovery and structure determination of the two new natural products in the margin. Both compounds were discovered in ocean sponges, one from Indonesia and one from a fungus living in a sponge common in the Pacific and Indian oceans. Both structures were determined largely by NMR and in neither case was an X-ray structure necessary. You should feel a bit more in tune with the chemists who deduced these structures as they look much simpler than Taxol or even than penicillin. We hope you will feel by the end of this chapter that you can tackle structural problems of this order of complexity with some confidence. You will need practice, and in this area above all it is vital that you try plenty of problems. Use the examples in the text as worked problems: try to solve as much as you can before reading the answer—you can do this only the first time you read because next time you will have your memory as a prompt.

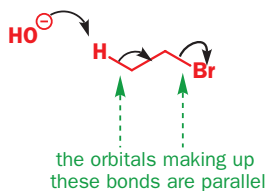
The stereochemistry at two of the stereogenic centres of chlorocarolide was unknown when this structure was published—stereochemistry is one of the hardest aspects of structure to determine. Nonetheless, NMR is second only to X-ray in what it tells us of stereochemistry, and we shall look at what coupling constants (J values) reveal about configuration, conformation, and reactivity. The first aspect we consider is the determination of conformation in six-membered rings.

3J values vary with H–C–C–H dihedral angle

Remember

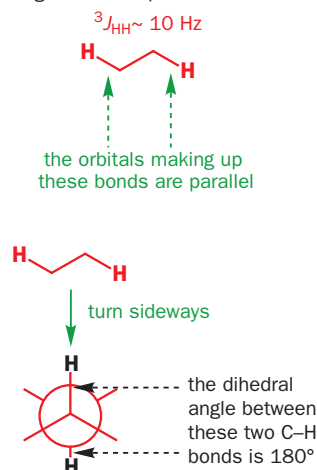
Parallel orbitals interact best.

best arrangement for E2 elimination



In the last chapter, we looked at some stereospecific eliminations to give double bonds, and you know that E2 elimination reactions occur best when there is an anti-periplanar arrangement between the proton and the leaving group.

largest 3J from parallel orbitals



In the NMR spectrum, coupling between protons arises from through-bond and not through-space interactions: *trans* coupling in alkenes is *bigger* than *cis* coupling (see Chapter 11, p. 269). So the same arrangement that leads to the best reaction ought also to lead to the largest coupling constant. In other words, if we replace 'Br' in the diagram with a second hydrogen atom but keep the orbital alignment the same, we ought to get the biggest possible coupling constant for a saturated system.

The usual description of this situation is in terms of the dihedral angle between the H–C–C–H bonds. The dihedral angle is obvious in the Newman projection as it is the angle between the two C–H bonds projected on a plane orthogonal to the C–C bond. In a Newman projection this plane is the plane of the paper, and here the angle is 180°.

When the dihedral angle is zero, the two C–H bonds are again in the same plane but not perfectly parallel. The coupling constant is again large, but not so large as in the previous case. In fact, the two arrangements are very like *cis* and *trans* double bonds, but the C atoms are tetrahedral not trigonal.

You may guess that, when the dihedral angle is 90°, the coupling constant is zero. What happens in between these extremes was deduced by Karplus in the 1960s and the relationship is usually known as the **Karplus equation**. It is easiest to understand from a graph of J against dihedral angle.

Examine this graph carefully and note the basic features as you will need them as we go through the chapter. These features are:

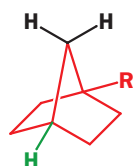
- Coupling is largest at 180° when the orbitals of the two C–H bonds are perfectly parallel
- Coupling is nearly as large at 0° when the orbitals are in the same plane but not parallel
- Coupling is zero when the dihedral angle is 90°—orthogonal orbitals do not interact
- The curve is flattened around 0°, 90°, and 180°— J varies little in these regions from compound to compound
- The curve slopes steeply at about 60° and 120°— J varies a lot in this region with small changes of angle and from compound to compound
- Numerical values of J vary with substitution, ring size, etc., but the Karplus relationship still works—it gives good *relative* values

These ideas come to life in the determination of conformation in six-membered rings. *Trans* diaxial hydrogen atoms are aligned with a dihedral angle of 180° and give the largest J values.

The other two situations, where one or both hydrogen atoms are equatorial, both have angles of about 60°, though axial/equatorial couplings are usually slightly larger than equatorial/equatorial ones.

Now for some illustrations. The simple cyclohexyl ester has just one substituent, which we expect to be equatorial (Chapter 18). The black hydrogen therefore has four neighbours—two axial Hs and two equatorial Hs. We expect to see a triplet from each and that the axial/axial coupling constant will be large. In fact, there is a 1H signal at δ 4.91, it is a tt (triplet of triplets) with $J = 8.8$ and 3.8 Hz. Only an axial H can have couplings as big as 8.8 Hz, so now we *know* that the ester is equatorial.

By contrast, the next ester, which also has only one substituent, has a 1H signal at δ 6.0 p.p.m. which is a simple triplet with $J = 3.2$ Hz. With no large couplings this cannot be an axial proton and the *substituent* must now be axial. It so happens that the small equatorial/axial and equatorial/equatorial couplings to the green hydrogens are the same. This is not so surprising as the dihedral angles are both 60°.



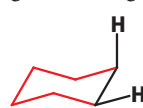
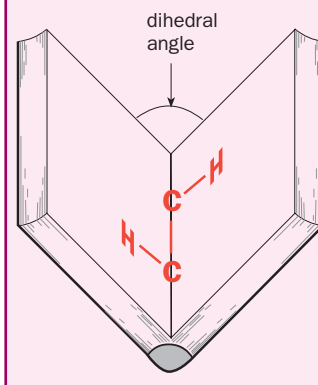
None of the dihedral angles in a six-membered ring are 90°, but in some bicyclic systems they are. Norbornane-type structures (bicyclo[2.2.0]heptanes), for example, typically have couplings of 0 Hz between the protons shown in black and green because the H–C–C–H dihedral angle is 90°.

The determination of *conformation* by NMR may more importantly allow us to

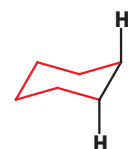
two C–H bonds are eclipsed in the plane of the paper – dihedral angle = 0°



As a reminder, the dihedral angle is most easily visualized by imagining the C–C bond lying along the spine of a partially-opened book. If the C–H bonds are written one on one page and the other on the other, then the dihedral angle is the angle between the pages of the book.



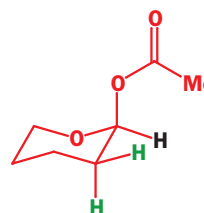
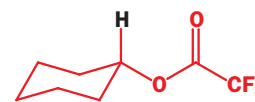
axial/equatorial Hs
dihedral angle 60°
 $^3J \sim 3\text{--}5$ Hz



diaxial Hs
dihedral angle 180°
 $^3J \sim 10\text{--}12$ Hz

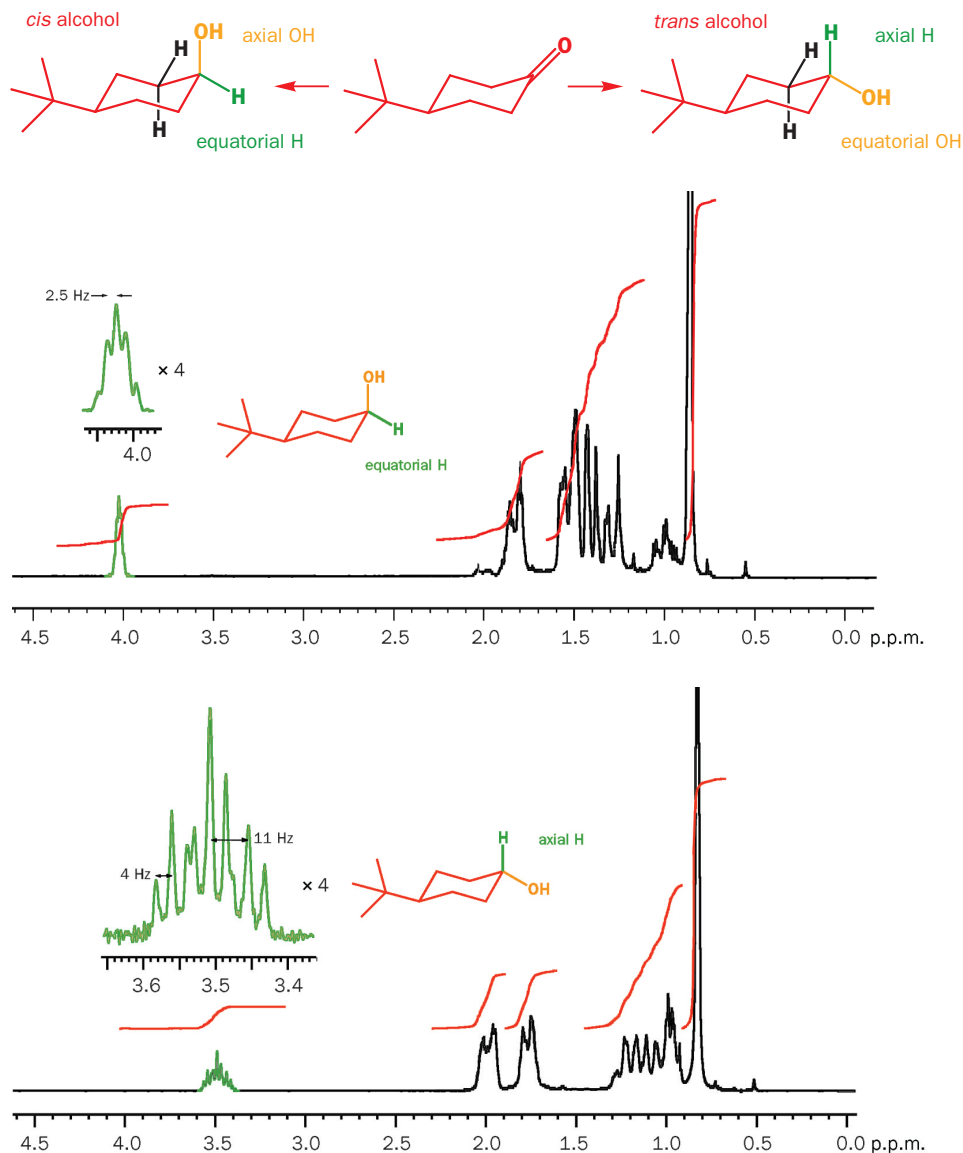


diequatorial Hs
dihedral angle 60°
 $^3J \sim 2\text{--}3$ Hz



We discuss in Chapter 42 why this substituent prefers to be axial.

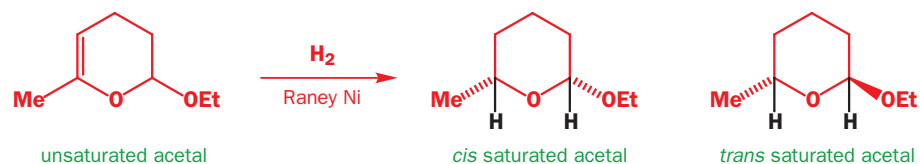
determine *configuration* at the same time. This often occurs when there are two or more substituents on the ring. Here is a simple example: you saw in Chapter 18 that the reduction of 4-*t*-butylcyclohexanone can be controlled by choice of reagent to give either a *cis* or a *trans* alcohol. It is easy to tell them apart as the *t*-butyl group will always be equatorial.



▶ You can draw a general conclusion from this observation: an NMR signal is roughly as wide as the sum of all its couplings. In any given compound, an axial proton will have a much *wider* signal than an equatorial proton.

The NMR spectrum of the green H is quite different in the two cases. Each has two identical axial neighbours and two identical equatorial neighbours (two are shown in black—there are two more at the front). Each green H appears as a triplet of triplets. In the *cis* alcohol both couplings are small (2.72 and 3.00 Hz) but in the *trans* alcohol the axial/axial coupling is much larger (11.1 Hz) than the axial/equatorial (4.3 Hz) coupling.

Hydrogenation of the double bond in this unsaturated acetal gives the saturated compound as a single isomer. But which one? Are the two substituents, Me and OEt, *cis* or *trans*?



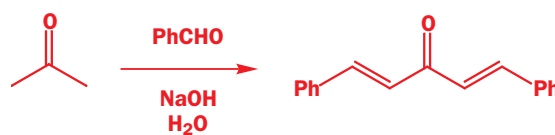
The appearance of the two black hydrogens in the NMR spectrum reveals the answer and also shows what conformation the molecule adopts. There is a 1H signal at 3.95 p.p.m. (which is therefore next to oxygen) and it is a double quartet. It must be the hydrogen next to the methyl group because of the quartet coupling. The quartet coupling constant has the 'normal' J value of 6.5 Hz. The doublet coupling is 9 Hz and this is too large to be anything other than an axial/axial coupling. This hydrogen is axial.

There is another 1H signal at 4.40 p.p.m. (next to two oxygens) which is a double doublet with $J = 9$ and 2 Hz). This must also be an axial proton as it shows an axial/axial (9 Hz) and an axial/equatorial coupling. We now know the conformation of the molecule.

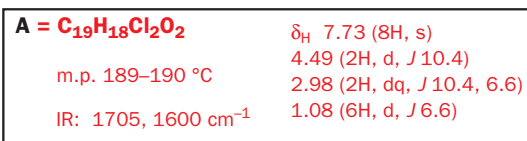
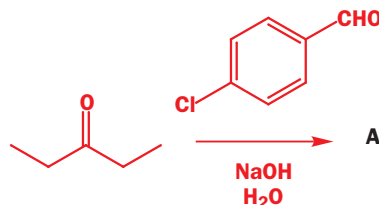
Both black hydrogens are axial so both substituents are equatorial. That also means in this case that they are *cis*. But note that this is because they are both on the same, upper side of the ring, not because they are both equatorial! The hydrogen at the front has two neighbours—an axial (brown) H, $J = 9$, and an equatorial (green) H, $J = 2$ Hz. All this fits the Karplus relationship as expected. You may have spotted that the H at the back appears to be missing a small coupling to its equatorial neighbour. No doubt it does couple, but that small coupling is not noticed in the eight lines of the double quartet. Small couplings can easily be overlooked.

When this compound is allowed to stand in slightly acidic ethanol it turns into an isomer. This is the *trans* compound and its NMR spectrum is again very helpful. The proton next to the methyl group is more or less the same but the proton in between the two oxygen atoms is quite different. It is at 5.29 p.p.m. and is an unresolved signal of width about 5 Hz. In other words it has no large couplings and must be an equatorial proton. The conformation of the *trans* compound is shown in the margin.

Now for a surprising product, whose structure and stereochemistry can be determined by NMR. Normally, reaction of a symmetrical ketone such as acetone with an aromatic aldehyde and base gives a double aldol condensation product in good yield.



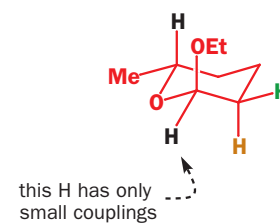
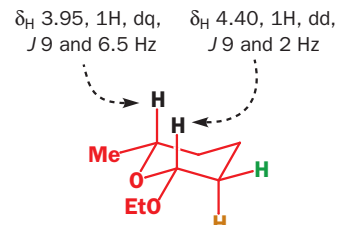
But in one particular case, the reaction between pentan-2-one and 4-chlorobenzaldehyde, a different product is formed. The mass spectrum shows that two aldehydes have reacted with one ketone as usual, but that only one molecule of water has been lost. Some of what we know about this compound is shown in the scheme.



The ^{13}C NMR spectrum shows that there is one ketone carbonyl group, as expected, but no alkene carbons. There is only one set of ^{13}C signals for the 4-Cl-phenyl ring and only two other carbons. This must mean that the molecule is symmetrical.

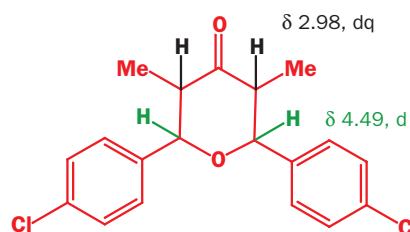
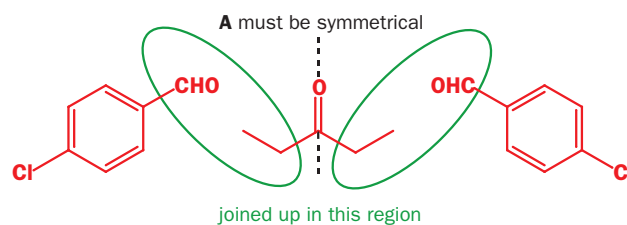
The three molecules must be joined up somewhere in the region marked. But how can we lose only one molecule of water and keep the symmetry?

The proton NMR spectrum gives the answer. Both methyl groups are still there, and they are identical, so we have two identical MeCH fragments. These CH protons (black) are *double quartets* so they have another neigh-



this H has only small couplings

■ You met this reaction in Chapter 28.



bour, the only remaining aliphatic proton (actually again two identical protons, in green) at δ_{H} 4.49 p.p.m. These protons must be next to both oxygen and the aromatic ring to have such a large shift. But there is only one spare oxygen atom so the protons at 4.49 p.p.m. must be next to the same oxygen atom—the structure is shown on the previous page.

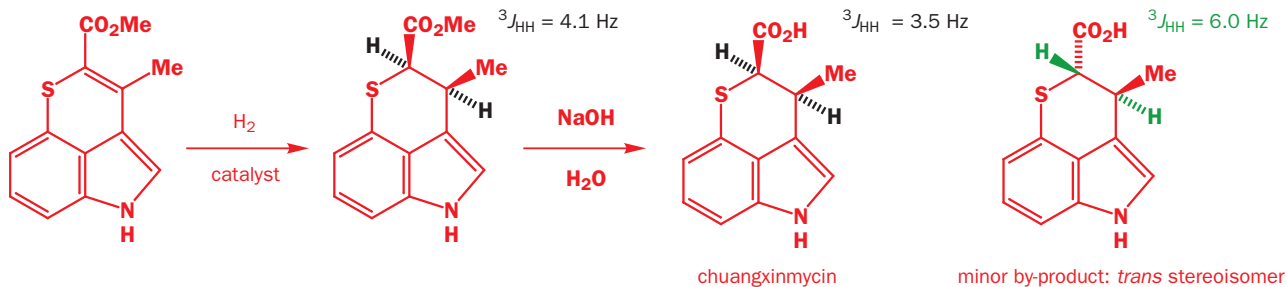
All that remains is the stereochemistry. There are four stereogenic centres but because of the symmetry only two structures are possible. Both methyl groups must be on the same side and both aryl rings must be on the same side.

The coupling constant between the hydrogen atoms is 10.4 Hz and so they must both be axial.

This means that the molecule has this structure and it is the *trans* compound: all the substituents are equatorial so it is the most stable structure possible.

Only fully saturated six-membered rings are really chairs or boats. Even with one double bond in the ring, the ring is partly flattened: here we will look at an even flatter example. A unique antibiotic has been discovered in China and called ‘chuangxinmycin’ (meaning ‘a new kind of mycin’ where mycin = antibiotic). It is unique because it is a sulfur-containing indole: few natural products and no other antibiotics have this sort of structure.

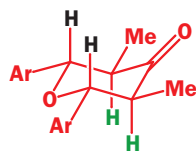
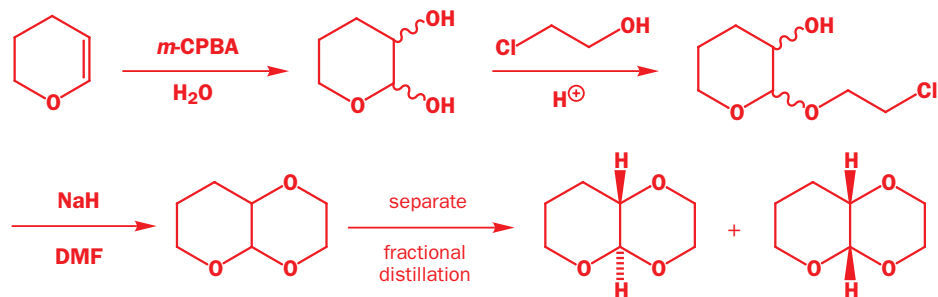
The structure itself was easy to elucidate, but the stereochemistry of the two black hydrogens was not so obvious. The coupling constant (3J) was 3.5 Hz. During attempts to synthesize the compound, Kozikowski hydrogenated the alkene ester below to give an undoubted *cis* product.



The 3J coupling between the black hydrogens in this compound was 4.1 Hz, much the same as in the antibiotic and, when the ester group was hydrolysed in aqueous base, the main product was identical to natural chuangxinmycin. However, there was a minor product, which was the *trans* isomer. It had $^3J = 6.0$ Hz. Note how much smaller this value is than the axial/axial couplings of 10 Hz or more in saturated six-membered rings. The flattening of the ring reduces the dihedral angle, reducing the size of J .

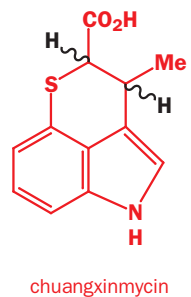
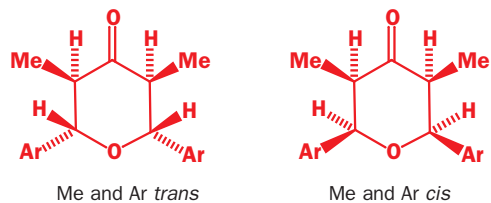
Stereochemistry of fused rings

Where rings are fused together (that is, have a common bond) determination of conformation may allow the determination of ring junction stereochemistry as well. Both isomers of this bicyclic ether were formed as a mixture and then separated.

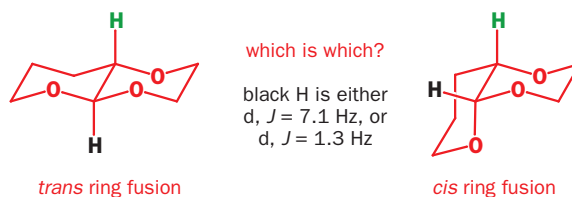


■ We looked at the conformations of cyclohexenes and cyclohexene oxides in Chapter 18, and we will look again at the stereochemistry of reactions of six-membered rings containing double bonds in Chapter 33.

▶ Hydrogenation is *cis*-selective: see Chapter 24.

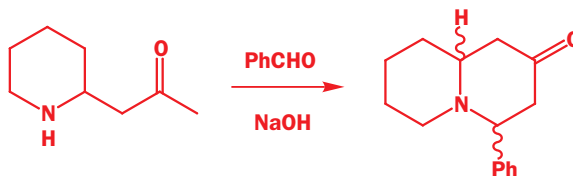


One proton at the ring junctions appears clearly in the NMR spectrum as it is next to two oxygen atoms (shown in black on the conformational diagrams alongside). In one compound it is a doublet, $J = 7.1$ Hz, and in the other a doublet $J = 1.3$ Hz. Which is which?

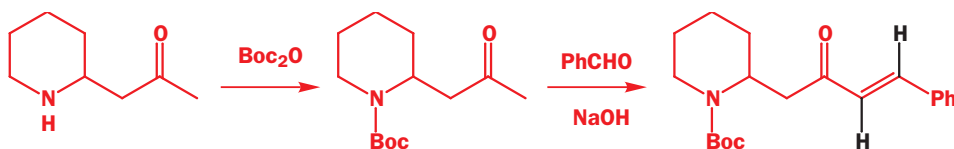


The coupling is to the green proton in each case and the dihedral angles are 180° for the *trans* compound but only 60° for the *cis* one, so the smaller coupling belongs to the *cis* compound. We shall discuss below why the *absolute* values are so low: this example illustrates how much easier stereochemical determination is if you have both stereoisomers to compare.

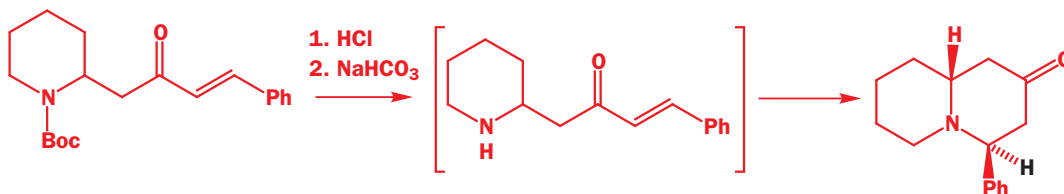
In the next example, unlike the last one, it eventually proved possible to make both compounds in high yield. But first the story: reaction of an amino-ketone with benzaldehyde in base gave a mixture of diastereoisomers of the product.



In unravelling the mechanism of the reaction, chemists protected the nitrogen atom with Boc (Chapter 25) before the reaction with benzaldehyde and found that a new product was formed that was clearly an *E*-alkene as its NMR spectrum contained $\delta_{\text{H}} 6.73$ (1H, d, $J 16$). This is too large a coupling constant even for axial/axial protons and can be only *trans* coupling across a double bond. They quickly deduced that a simple aldol reaction had happened.

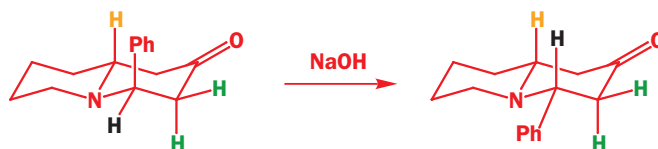


When the Boc protecting group was removed, the cyclization reaction occurred under very mild conditions but now a *single* diastereoisomer of the product was formed.

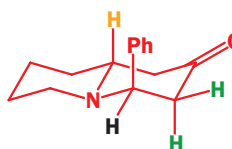


This isomer had one proton that could be clearly seen at $\delta_{\text{H}} 4.27$ p.p.m.—well away from all the rest. This is the proton marked in black between nitrogen and the phenyl group. It was a double doublet with $J = 6$ and 4 Hz. Neither of these is large enough to be an axial/axial coupling but 6 Hz is within the range for axial/equatorial and 4 Hz for equatorial/equatorial coupling. The compound must have the conformation shown in the margin.

Treatment of this product with stronger base (NaOH) isomerized it to a compound in which the same proton, now at $\delta_{\text{H}} 3.27$ p.p.m., was again a double doublet but with $J = 10$ and 5 Hz. It is now an axial proton so the new conformation is this.

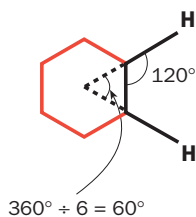


Notice that we have confidently assigned the configuration of these compounds without ever being able to 'see' the yellow proton at the ring junction. Since nitrogen can invert rapidly, we know that this decalin-like structure will adopt the more stable *trans* arrangement at the ring junction.

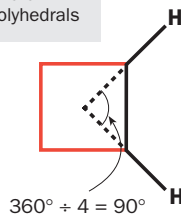


Couplings around double bonds were discussed in Chapter 11, p. 269.

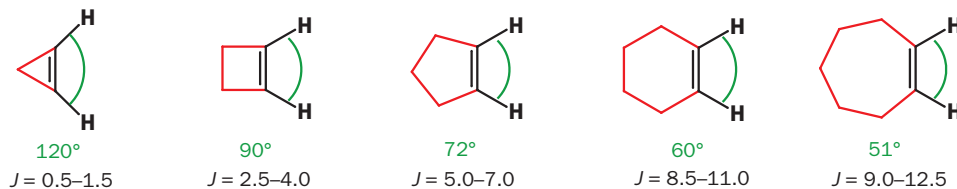
The dihedral angle is not the only angle worth measuring



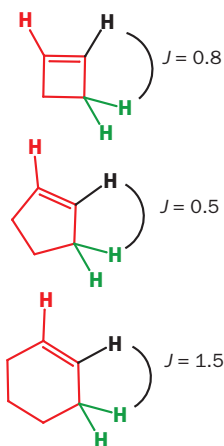
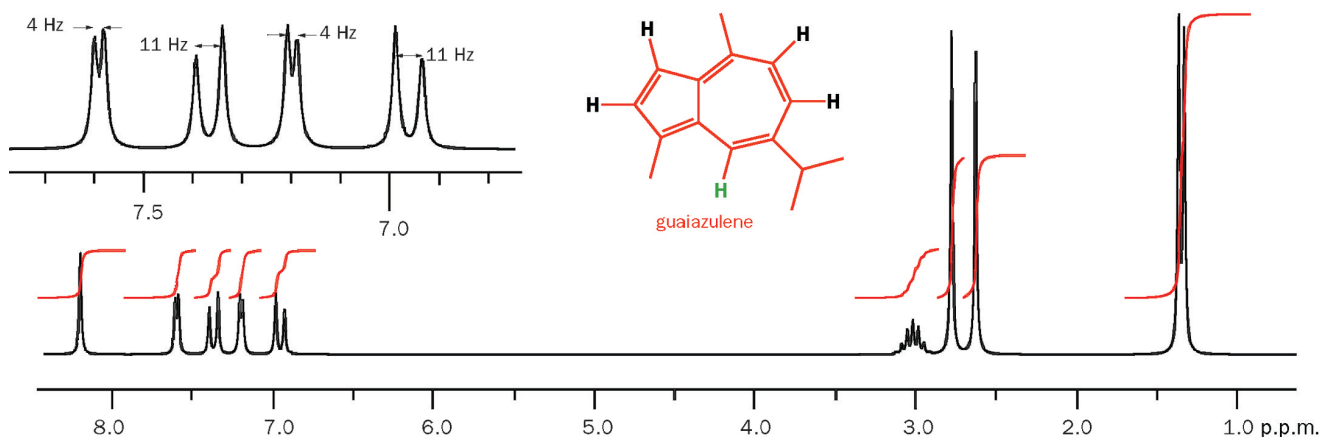
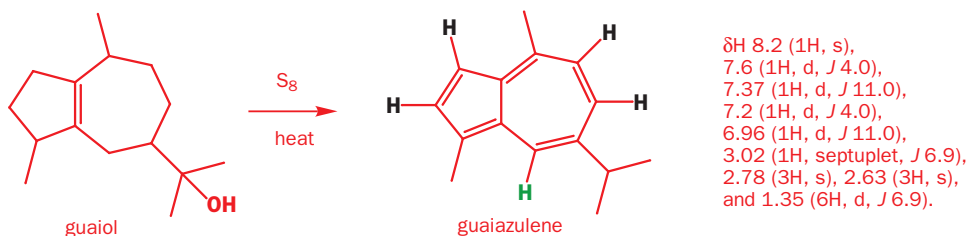
These would be the angles if the structures were regular, planar polyhedrals



We should also consider how the two C–H bonds are spread out in space. The dihedral angle is what we see when we look down the spine of the book in our earlier analogy (p. 825)—now we want to look at the pages in the normal way, at right angles to the spine, as if we were going to read the book. We can show what we mean by fixing the dihedral angle at 0° (the C–H bonds are in the same plane) and looking at the variation of J with the ring size of cyclic alkenes.



The wider apart the hydrogens are spread, the smaller the coupling constant. Remember, the dihedral angle stays the same (0°)—we are just varying the angle in the plane. A dramatic illustration of this comes with the product of dehydrogenation of the natural product guaiol with elemental sulfur. From the brown, smelly reaction mixture, guaiazulene, a deep blue oil, can be distilled.



Some assignments are clear. The 6H doublet and the 1H septuplet are the isopropyl group and the two 3H singlets belong to the two methyl groups—we can't really say which belongs to which. The 1H singlet must be the green hydrogen as it has no neighbours and that leaves us with two coupled pairs of protons. One pair has $J = 4$ Hz and the other $J = 11$ Hz. We expect to find larger coupling where the H–C–C–H angle is smaller, so we can say that the 4 Hz coupling is between the pair on the five-membered ring and the 11 Hz coupling is between the pair on the seven-membered ring.

When protons on a double bond in a ring have neighbours on saturated carbon, the coupling constants are all small and for the same reason—the angles in the plane of the ring are approaching 90° even though the dihedral angles are $45\text{--}60^\circ$ in these examples. A bizarre result of this is that the 3J coupling between the red and black hydrogens is often about the same as the allylic (4J) coupling between the red and the green hydrogens. An example follows in a moment.

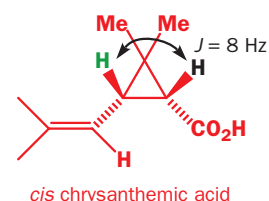
Vicinal (3J) coupling constants in other ring sizes

The ‘spreading out’ effect also affects vicinal (3J) couplings in simple saturated rings. No other ring size has so well defined a conformation as that of the six-membered ring. We can still note useful trends as we move from 6 to 5 to 4 to 3. Briefly, in five-membered rings, *cis* and *trans* couplings are about the same. In four- and three-membered rings, *cis* couplings are larger than *trans*. But in all cases the absolute values of J go down as the ring gets smaller and the C–H bonds are ‘spread out’ more. Indeed, you can say that *all* coupling constants are smaller in small rings, as we shall see. We need to examine these cases a bit more.

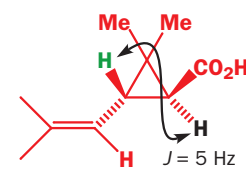
Three-membered rings

Three-membered rings are flat with all bonds eclipsed so the dihedral angle is 0° for *cis* Hs and 109° for *trans* Hs. Looking at the Karplus curve, we expect the *cis* coupling to be larger, and it is. A good example is chrysanthemic acid, which is part of the pyrethrin group of insecticides found in the pyrethrum plant. Both *cis* and *trans* chrysanthemic acids are important.

In both isomers the coupling between the green proton on the ring and its red neighbour on the double bond is 8 Hz. In the *cis* compound, the green proton is a triplet so the *cis* coupling in the ring is also 8 Hz. In the *trans* compound it is a double doublet with the second coupling, *trans* across the ring to the black H, of 5 Hz.

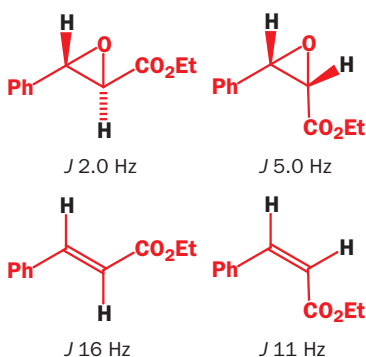


cis chrysanthemic acid



trans chrysanthemic acid

The most important three-membered rings are the epoxides. You saw in Chapter 11 (p. 269) that electronegative atoms reduce coupling constants by withdrawing electron density from the bonds that transmit the coupling ‘information’. This means that epoxide couplings are very small—much smaller than those of their closely related alkenes, for example. Compare the four coupling constants



in the diagram: for the epoxide, all couplings are small, but *cis* coupling is larger than *trans* coupling. In alkenes, *trans* coupling is larger (Chapter 11, p. 269). The table summarizes the coupling constants for alkenes, epoxides, and cyclopropanes.

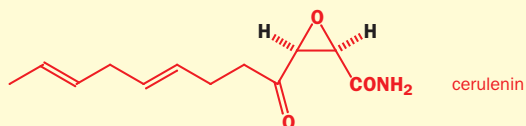
Coupling constants J , Hz

Stereochemistry	Alkene	Cyclopropane	Epoxide
<i>cis</i>	10–12	8	5
<i>trans</i>	14–18	5	2

▶ The epoxides have much smaller coupling constants because: (1) the C–C bond is longer; (2) there is an electronegative element; and (3) the ‘spreading out’ effect of the small ring comes into play.

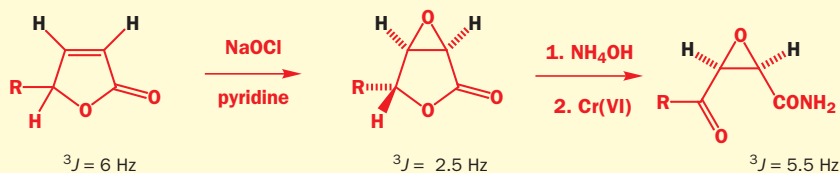
Cerulenin

The natural product cerulenin is an antibiotic containing a *cis* epoxide. The coupling constant between the black hydrogens is 5.5 Hz.



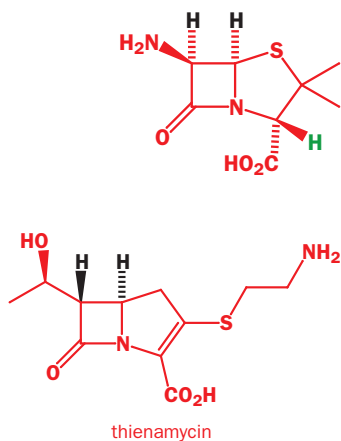
The compound has been made from an unsaturated lactone by epoxidation and ring opening. Follow what

happens to the coupling constant between the black hydrogens as this sequence develops.



The *cis* coupling in the alkene is small because it is in a five-membered ring. It gets smaller in the bicyclic epoxide because the black Hs are now in both five- and three-

membered rings and both are next to oxygen, but it gets larger in cerulenin itself because the five-membered ring has been opened.



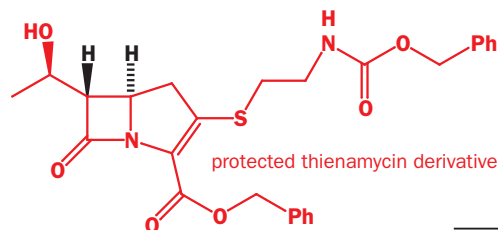
Four-membered rings

A similar situation exists with four-membered rings—the *cis* coupling is larger than the *trans* but they are generally both smaller than those in larger rings. A good example is the amino acid in the margin, the skeleton of the penicillins. The NMR spectrum contains three ^1H signals in the middle regions. There is a singlet at δ_{H} 4.15 p.p.m. that clearly belongs to the isolated green proton and two doublets at δ_{H} 4.55 and 5.40 p.p.m. that must belong to the black protons. The coupling constant between them is 5 Hz and they are *cis*-related.

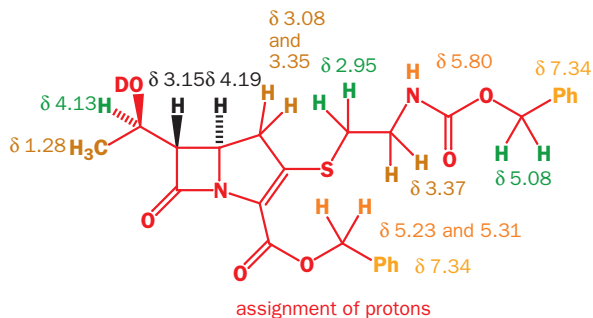
There are now large numbers of β -lactam antibiotics known and one family has the opposite (*trans*) stereochemistry around the four-membered ring. The typical member is thienamycin. We will analyse the spectrum in a moment, but first look at the differences—apart from stereochemistry—between this structure and the last. The sulfur atom is now outside the five-membered ring, the acid group is on a double bond in the same ring, and the amino group has gone from the β -lactam to be replaced by a hydroxyalkyl side chain.

Turning to the spectrum and the key question of stereochemistry, this is what the Merck discoverers said in their original article: ^1H NMR spectra of thienamycin (and derivatives) . . . show small vicinal coupling constants $J \leq 3$ Hz for the two β -lactam hydrogens. Past experience with penicillins . . . shows the *cis* relationship of the β -lactam hydrogens to be always associated with the larger coupling.’ As we have just seen penicillins have $J \sim 5$ Hz for these hydrogens.

The NMR spectrum of a thienamycin derivative with protecting groups on the amine and carboxylic acids is shown below. Try your hand at interpreting it before you read the explanation below. Your aim is to find the coupling constant across the four-membered ring.



The simple answer is 2.5 Hz. The signals at 3.15 and 4.19 p.p.m. are the protons on the β -lactam ring and the 9 Hz extra coupling is to the CH_2 in the five-membered ring. If you went into this spectrum in detail you may have been worried about the 12.5 and especially the 18 Hz couplings. These are 2J (geminal) couplings and we will discuss them in the next section.



The full assignment is shown above.

We should emphasize that a coupling constant of 5 or 2.5 Hz in isolation would not allow us to assign stereochemistry across the four-membered ring but, when we have both, we can say with confidence that the larger coupling is between *cis* Hs and the smaller coupling between *trans* Hs.

NMR spectrum of thienamycin derivative in CD_3OD

Shift (δ_{H}), p.p.m.	Integration	Multiplicity	Coupling constants (J), Hz
1.28	3H	d	6.5
2.95	2H	m	not resolved
3.08	1H	dd	9, 18
3.15	1H	dd	2.5, 7
3.35	1H	dd	9, 18
3.37	2H	m	not resolved
4.13	1H	dq	7, 6.5
4.19	1H	dt	2.5, 9
5.08	2H	s	—
5.23 and 5.31	2H	AB system ^a	12.5
5.80	1H	broad	—
7.34	10 H	m	not resolved

^a See p. 271 for discussion of AB systems.

Five-membered rings

You can visualize the conformation of a five-membered ring simply as a chair cyclohexane with one of the atoms deleted. But this picture is simplistic because the five-membered ring flexes (rather than flips) and any of the carbon atoms can be the one out of the plane. All the hydrogen atoms are changing positions rapidly and the NMR spectrum ‘sees’ a time-averaged result. Commonly, both *cis* and *trans* couplings are about 8–9 Hz in this ring size.

The best illustration of the similarity of *cis* and *trans* couplings in five-membered rings is a structure that was incorrectly deduced for that very reason. Canadensolide is an antifungal compound found in a *Penicillium* mould. The gross structure was quite easy to deduce from the mass spectrum, which gave the formula $C_{11}H_{14}O_4$ by exact mass determination; the infrared, which showed (at 1780 and 1667 cm^{-1}) a conjugated 5-ring lactone; and some aspects of the proton NMR. The proposed structure is shown alongside.

The stereochemistry of the ring junction Hs (shown in black and green) is not in question. They are certain to be *cis* as it is virtually impossible for two five-membered rings to be fused *trans*. The stereochemistry in question involves the third stereogenic centre on the left-hand ring. The coupling constant between the black and green Hs is 6.8 Hz, while that between the green and brown Hs is 4.5. Is this different enough for them to be *trans*? The original investigators decided that it was.

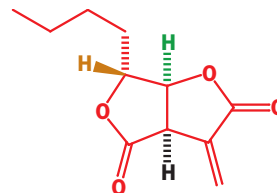
The mistake emerged when some Japanese chemists made this compound by an unambiguous route. The NMR spectrum was quite like that of canadensolide, but not the same. In particular, the coupling between the green and brown Hs was 1.5 Hz—quite different! So they also made the other possible diastereoisomer and found that it was identical to natural canadensolide. The details are in the margin.

An example of vicinal coupling in structural analysis: aflatoxins

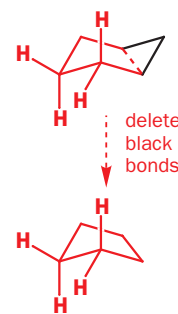
We can bring together a lot of these points in the structure of one compound, the dreaded aflatoxin. Aflatoxin B_1 is an example.

The four red protons on saturated carbons in the five-membered ring in the margin appear as two triplets: δ_H 2.61 (2H, t, J 5 Hz) and δ_H 3.42 (2H, t, J 5 Hz). The *cis* and *trans* couplings are the same. The yellow proton on the left, on the junction between the two five-membered cyclic ethers, is a doublet δ_H 6.89 (1H, d, J 7 Hz). This is, of course, the *cis* coupling to the black hydrogen. The black hydrogen has this coupling too, but it appears as a doublet of triplets with a triplet coupling of 2.5 Hz: δ_H 4.81 (1H, dt, J 7, 2.5, 2.5 Hz). These small couplings can only be to the two green hydrogens: the 3J and 4J couplings are indeed the same.

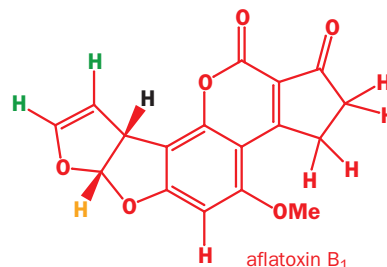
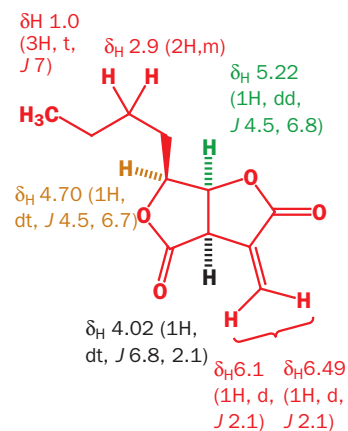
Finally there is another strange coincidence—each green hydrogen appears as a triplet with 2.5 Hz couplings. Evidently, the *cis* coupling across the double bond is also 2.5 Hz. We expect *cis* coupling in a cyclopentene to be small (it was 4 Hz in the azulene on p. 830), but not that small—it must be the electronegative oxygen atom that is reducing the value still further.



proposed structure for canadensolide



You can convince yourself of this by making a model.



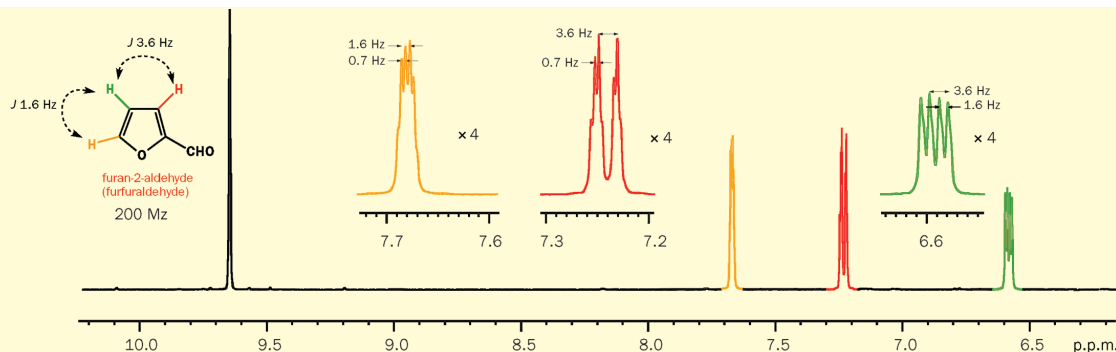
aflatoxin B_1

► Aflatoxins

Aflatoxins were mentioned in Chapter 20: they occur in moulds, including those that grow on some foods, and cause liver cancer. These slow-acting poisons are among the most toxic compounds known.

Coupling in furans

The size of coupling constants in five-membered rings containing oxygen is illustrated clearly in furfuraldehyde (furan-2-aldehyde): note how small the couplings are.



Geminal (2J) coupling

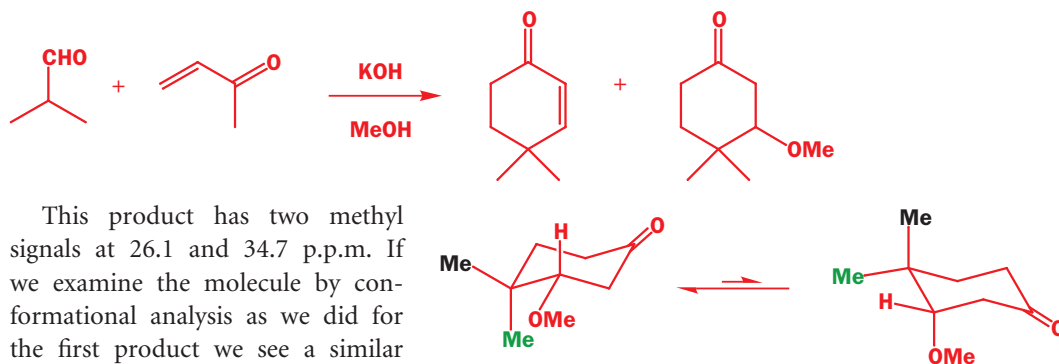
For coupling to be seen, the two hydrogen atoms in question must have different chemical shifts. For 2J couplings the two hydrogen atoms are on the same carbon atom, so in order to discuss geminal coupling we must first consider what leads the two hydrogens of a CH_2 group to have different shifts.

To introduce the topic, an example. It may seem to you that any six-membered ring might show different chemical shifts for axial and equatorial groups. But this doesn't happen. Consider the result of this Robinson annelation reaction.



The two methyl groups at C4 give rise to a single signal in the ^{13}C NMR at 27.46 p.p.m. Even though one of them is (pseudo)axial and one (pseudo)equatorial, the molecule exists in solution as a rapidly equilibrating mixture of two conformations. The axial green methyl in the left-hand conformer becomes equatorial in the right-hand conformer, and vice versa for the black methyl group. This exchange is rapid on the NMR time-scale and the equilibrium position is 50:50. Time averaging equalizes the chemical shifts of the two methyl groups, and the same is true for the CH_2 groups around the back of the ring.

However, the enone is not the only product of this reaction. A methanol adduct is also formed by Michael addition of methanol to the conjugated enone.

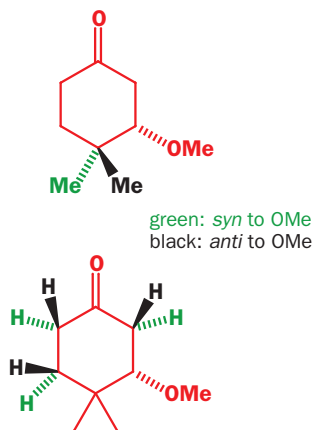


This product has two methyl signals at 26.1 and 34.7 p.p.m. If we examine the molecule by conformational analysis as we did for the first product we see a similar situation.

Similar but not the same. This time, the two conformations are not identical. One has the OMe group equatorial and the other has it axial. Even the two methyl groups do not entirely change places in the two conformations. True, the green methyl is axial on the left and equatorial on the right, but it has a gauche (dihedral angle 60°) relationship with the OMe group in *both* conformations. The black Me group is gauche to OMe on the left but anti-periplanar to the OMe group on the right. When two different conformations, in each of which the black and green methyl groups are different (that is, they don't just change places), are averaged, the two methyl groups are not equalized.

Perhaps a simpler way to discover this is to use a configurational, rather than a conformational, diagram. The green methyl group is on the same face of the molecule as the MeO group, while the black methyl group is on the other face. No amount of ring flipping can make them the same. They are *diastereotopic*, a term we shall define shortly. And so are all three CH_2 groups in the ring. The green Hs are on the same face of the molecule as the MeO group while the black Hs are on the other face.

A proton NMR example confirms this, and here is one from an odd source. There are fungi that live on animal dung, called coprophilous fungi. They produce antifungal compounds, presumably to



fight off competition! Anyway, in 1995 two new antifungal compounds were discovered in a fungus living on lemming dung. They were named coniochaetones A and B and their structures were deduced with the usual array of mass and NMR spectra. The proton spectra, run on a 600 MHz machine, are shown below, and they reveal considerable detail.

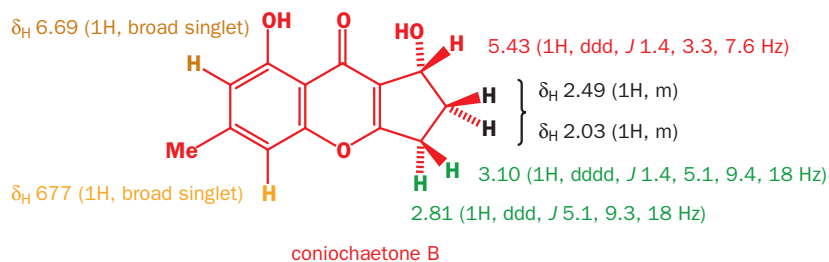
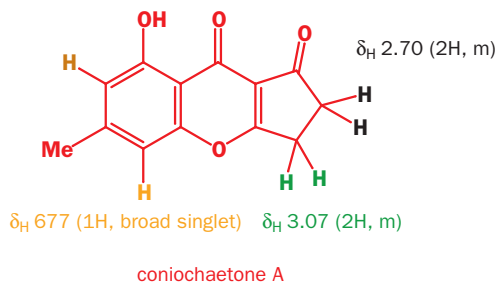
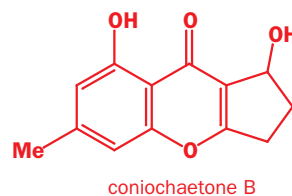
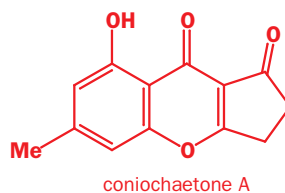
Coniochaetone A		Coniochaetone B	
δ_{H} , p.p.m.	Coupling	δ_{H} , p.p.m.	Coupling
2.41 (3H)	s	2.38 (3H)	s
		5.43 (1H)	ddd, J 1.4, 3.3, 7.6 Hz
2.70 (2H)	m	2.49 (1H)	m
		2.03 (1H)	m
3.07 (2H)	m	3.10 (1H)	dddd, J 1.4, 5.1, 9.4, 18 Hz
		2.81 (1H)	ddd, J 5.1, 9.3, 18 Hz
6.77 (1H)	broad s	6.70 (1H)	broad s
6.69 (1H)	broad s	6.62 (1H)	broad s
12.21 (1H) ^a	s	12.25 (1H) ^a	s

^a Exchanges with D₂O.

Some of the spectrum is essentially the same for the two compounds, but other parts are quite different. Coniochaetone A has a very simple spectrum, very easily assigned.

Coniochaetone B is rather more interesting. The spectrum is much more complicated, even though it has only one more C–H than coniochaetone A. The reason is that addition of that H atom creates a stereogenic centre and makes the top and bottom faces of the molecule different. Both CH₂ groups become diastereotopic.

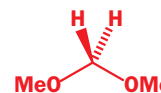
The green Hs are coupled to each other ($J = 18$ Hz) and to each of the black Hs with a different coupling constant. One of the green hydrogens also shows a long-range ($^4J = 1.4$ Hz) W-coupling to the red H. The black Hs are too complex to analyse, even at 600 MHz, but the different couplings to the red hydrogen are shown by the signal at 5.43 p.p.m.

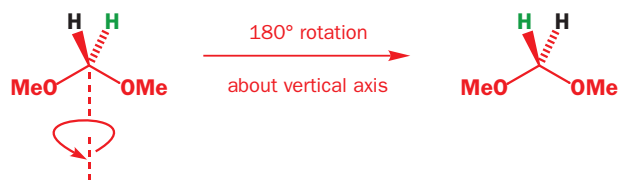


Diastereotopic CH₂ groups

The green protons in the last example couple to one another, so they must be different. Until this chapter, you may have thought it self-evident that two protons attached to the same carbon would be identical, but you have now seen several examples where they are not. It is now time to explain more rigorously the appearance of CH₂ groups in NMR spectra, and you will see that there are *three* possibilities. To do this, we shall have to discuss some aspects of symmetry that build on what you learned in Chapter 16.

First, an example in which the two hydrogens are indeed the same. We may draw one hydrogen coming towards us and one going away, but the two Hs are the same. This is easy to demonstrate. If we colour one H black and one green, and then rotate the molecule through 180°, the black H appears in the place of the green H and vice versa. The rotated molecule hasn't changed because the *other* two substituents (OMe here) are also the same.



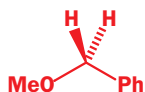


If we had given out uncoloured models of this molecule with this book, and asked each reader to paint one H green and one H black, we would have no way at all of giving instructions about which to paint what colour. But it wouldn't matter because, even without these instructions, every reader would produce an identical model, whichever way they painted their Hs.

The correct description for this pair of hydrogen atoms is **homotopic**. They are the same (*homo*) topologically and cannot be distinguished by chemical reagents, enzymes, NMR machines, or human beings. The molecule is achiral—it has no asymmetry at all.

● Homotopic groups

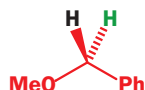
Homotopic groups cannot be distinguished by any means whatsoever: they are chemically entirely identical.



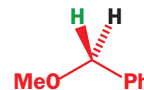
What happens when the other two substituents are different? At first sight the situation does not seem to have changed. Surely the two hydrogens are still the same as one another?

In fact, they aren't—not quite. If we had given out uncoloured models of this molecule and just said 'paint one H green and one H black', we would not have got just one type of model.

We would have got about 50% looking like this:



and 50% looking like this:

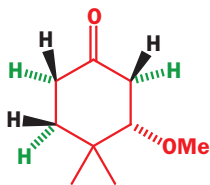


But this time, we *could* give instructions about which H we wanted which colour. To get the first of these two, we just need to say 'Take the MeO group in your *left* hand and the Ph group in your *right*, kink the carbon chain upwards. The hydrogen coming towards you is to be painted black.' All the models produced by readers would then be identical—as long as the readers knew their left from their right. This is a very important point: the green and black hydrogens in this molecule (unlike the first one) can be described only in phrases incorporating the words 'left' or 'right', and are distinguishable only by a system that knows its left from its right.

Human beings are such a system: so are enzymes, and the asymmetric reagents you will meet in Chapter 45. But NMR machines are not. NMR machines cannot distinguish right and left—the NMR spectra of two enantiomers are identical, for example. It is not a matter of enantiomers in the molecule in question—it has a plane of symmetry and is achiral. Nonetheless, the relationship between these two hydrogens is rather like the relationship between enantiomers (the two possible ways of colouring the Hs are enantiomers—mirror images) and so they are called **enantiotopic**. Enantiotopic protons appear identical in the NMR spectrum.

● Enantiotopic groups

Enantiotopic groups can be distinguished by systems that can tell right from left, but are still magnetically equivalent and appear identical in the NMR spectrum.



The third situation usually arises when the molecule has a stereogenic centre. As an example we can take the Michael product from the beginning of this section.

It is now very easy to distinguish the two hydrogens on each ring carbon atom and, if we want to give instructions on how to paint a model of this molecule, we can just say 'Make all the Hs on the same side of the ring as OMe green, and the ones on the opposite side to OMe black.' We do not need to use the words 'right' or 'left' in the instructions, and it is not necessary to

▶ To understand this discussion, it is very important that you appreciate points such as this which we covered in Chapter 16. You may need to refresh your memory of the stereochemical points there before you read further.

know your right from your left to tell the two types of Hs apart. Ordinary chemical reagents and NMR machines can do it. These Hs are different in the way that diastereoisomers are different and they are **diastereotopic**. We expect them to have different chemical shifts in the proton NMR spectrum.

The same is true of the methyl groups: they too are diastereotopic and we expect them to have different shifts.

● Diastereotopic groups

Diastereotopic groups are chemically different: they can be distinguished even by systems that cannot tell right from left, and they appear at different chemical shifts in the NMR spectrum.

How to tell if protons are homotopic, enantiotopic, or diastereotopic

What we have said so far explains to you why homotopic and enantiotopic groups appear identical in the NMR spectrum, but diastereotopic protons may not. Now we will give a quick guide to determining what sort of pair you are dealing with in a given molecule.

The key is to turn your molecules into two molecules. Replace one of the Hs (we'll assume we're looking at Hs, but the argument works for other groups too—Me groups, for example, as in the last example above) with an imaginary group 'G'. Write down the structure you get, with stereochemistry shown. Next, write down the structure you get by replacing the other H with the group G. Now the more difficult bit: identify the stereochemical relationship between the two molecules you have drawn.

- If they are identical molecules, the Hs are homotopic
- If they are enantiomers, the Hs are enantiotopic
- If they are diastereoisomers, the Hs are diastereotopic

This is really just a simpler way of doing what we did with black and green above, but it is easy to do for any molecule. Take the first of our examples, and replace each H in turn by G.

These two molecules are identical, because just turning one over gives the other: the protons are homotopic. Now for the next example.

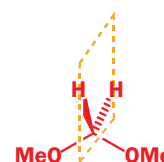
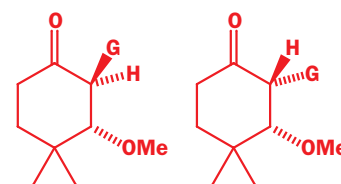
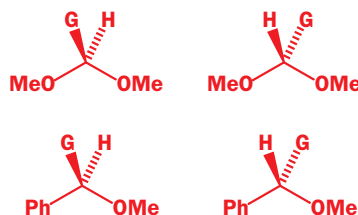
The two molecules are not identical: to make one into the other you need to reflect in the plane of the paper, so they are enantiomers, and the Hs are *enantiotopic*. There is another term we must introduce you to in relation to this molecule, which will become useful in the next chapter, and that is 'prochiral'. The molecule we started with here was not chiral—it had a plane of symmetry. But by changing just one of the Hs to a different group we have made it chiral. Molecules that are achiral but can become chiral through one simple change are called **prochiral**.

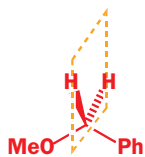
Now we will choose one of the three pairs of Hs in the cyclohexanone example. The starting molecule is, of course, now chiral, and the two molecules we get when we replace each H by G are now diastereoisomers: one has G and OMe *anti*, the other *syn*, and the pairs of hydrogens are *diastereotopic*.

Finally, one last look at symmetry in the three molecules. We will consider two planes as potential planes of symmetry—the plane that bisects the H–C–H angle of the two Hs we are interested in (this is the plane of the paper as we have drawn all three molecules), and a plane at right angles to that plane, passing through the carbon atom and both hydrogen atoms. This second plane is marked on the diagrams in yellow.

This molecule, the most symmetrical of the three, is achiral. The central carbon atom is completely nonstereogenic. Both planes are planes of symmetry and the hydrogens are homotopic. They are chemically and magnetically equivalent.

▶ NMR machines *can* tell the difference, but it does not follow that they *will*. There are many examples of protons that are different but have the same chemical shift (toluene, PhMe, shows a singlet in the NMR for all its aromatic protons even though they are of three different kinds). Sometimes diastereotopic protons have the same chemical shift, sometimes slightly different chemical shifts, and sometimes very different chemical shifts.





This slightly less symmetrical molecule is not chiral but *prochiral*. The carbon atom is a prochiral (or prostereogenic) centre. The plane of the paper is still a plane of symmetry, but the yellow plane containing the two H atoms is not and the hydrogen atoms are enantiotopic. They are magnetically equivalent and can be distinguished only by humans, enzymes, and other asymmetric reagents.

This least symmetrical molecule is chiral as it has a chiral (stereogenic) centre. The carbon atom we are discussing is not a stereogenic centre but is again a prochiral centre. Neither plane is a plane of symmetry and the hydrogen atoms are diastereotopic. They are chemically and magnetically different and can be distinguished by NMR or by chemical reagents.

Look back at the structures we have just been discussing and you should see that both the enone used to produce this molecule and coniochaetone A have a plane of symmetry bisecting their CH₂ groups while coniochaetone B does not. This gives another easy way of telling if a pair of groups will appear different in the NMR spectrum. If the plane passing through the carbon atom and bisecting the H–C–H bond angle (the plane of the paper in these diagrams) is a plane of symmetry, then the two Hs (which are reflected in that plane) are magnetically equivalent. (If they also lie in a plane of symmetry, they are homotopic; if they don't, they are enantiotopic.)

The shape of the NMR signal

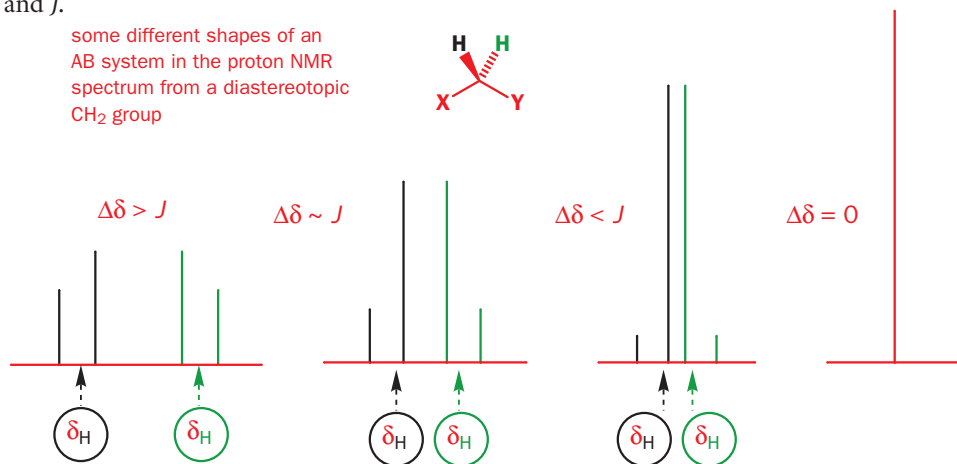
A prochiral CH₂ group with diastereotopic Hs isolated from any other Hs will give rise to two signals, one for each H, and they will couple to each other so that the complete signal is a pair of doublets. You would expect geminal coupling constants to be larger than vicinal ones simply because the Hs are closer—we are talking about ²*J* instead of ³*J* couplings. A typical vicinal (³*J*) coupling constant for a freely rotating open-chain system without nearby electronegative atoms would be 7 Hz. A typical geminal (²*J*) coupling constant is just twice this, 14 Hz.

The chemical shift differences ($\Delta\delta$) between Hs on the same carbon atom tend to be small—usually less than 1 p.p.m.—and the coupling constants *J* tend to be large so the signals usually have $\Delta\delta \sim J$ and are distorted into an AB pattern. The signal may have any of the forms indicated here, depending on the relative sizes of $\Delta\delta$ (the chemical shift difference between the peaks) and *J*.

■ The shape of NMR signals where *J* and the chemical shift difference are of the same order of magnitude were discussed in Chapter 11. The arguments apply to any coupled protons of similar chemical shift—there we used disubstituted aromatic rings as the example—but are particularly relevant here.

► It is not usually easy to decide which proton gives rise to which signal. This is not important in assigning the structure, but may be important in assigning stereochemistry. We shall discuss how to assign the protons shortly in relation to the conformation of six-membered rings, and then again later using the nuclear Overhauser effect.

some different shapes of an AB system in the proton NMR spectrum from a diastereotopic CH₂ group

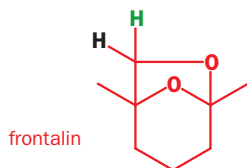


The coupling constant is always the difference in Hz between the two lines of the same colour in these diagrams, but the chemical shifts are not so easily measured. The chemical shift of each proton is at the weighted mean of the two lines—the more distorted the signal, the nearer the chemical shift to that of the larger inner line.

Examples of AB systems from diastereotopic CH₂ groups

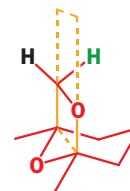
It is time to look at some examples. The insect pheromone frontalin can be drawn like this.

There is nothing wrong with this drawing except that it fails to explain why the black and green hydrogens are different and give a pair of doublets at δ_{H} 3.42 and 2.93 p.p.m., each 1H, *J* 7 Hz (an AB

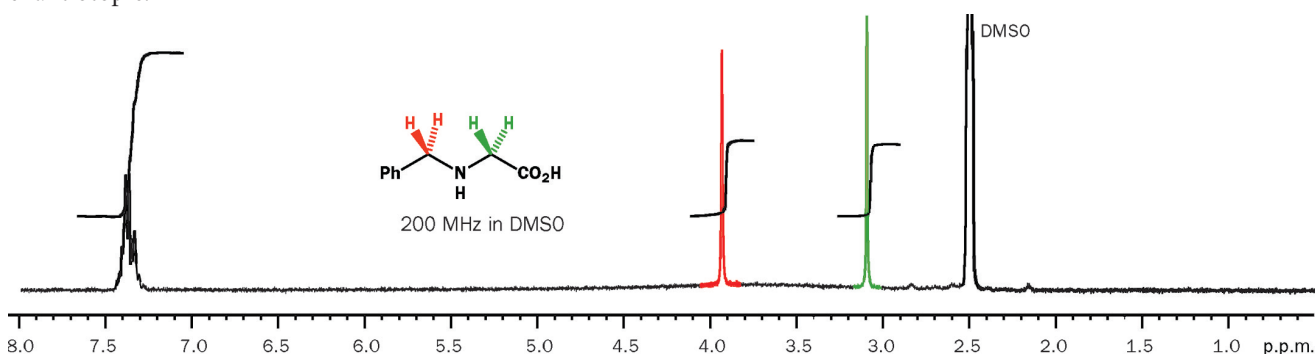
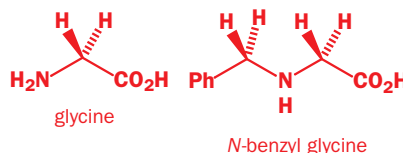


system) in the proton NMR. These protons must be diastereotopic. A conformational diagram should help.

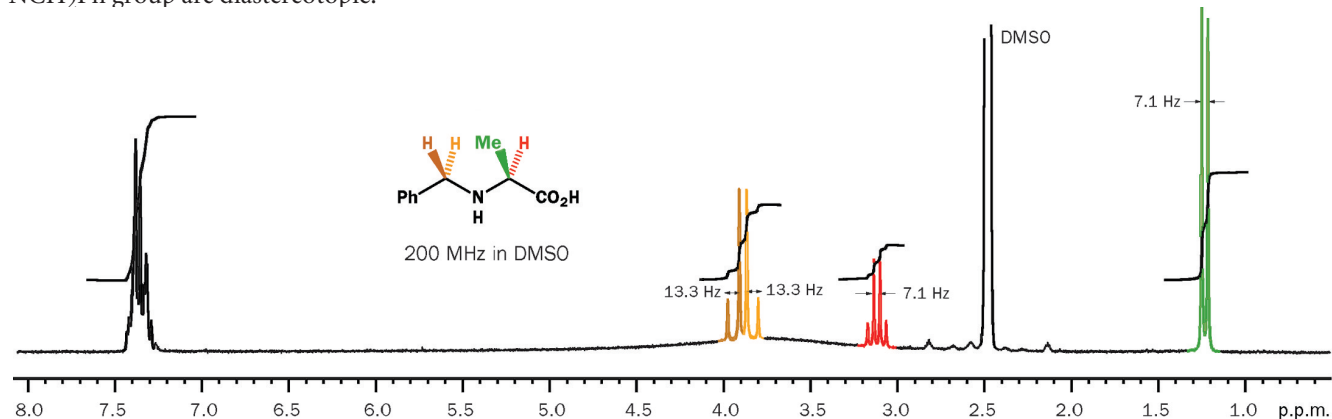
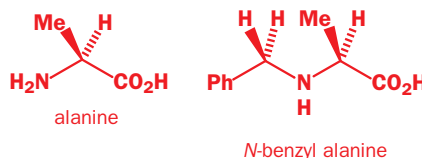
The vital H atoms are on a diaxial bridge across the six-membered ring. Under the black H is an oxygen atom, while under the green H is a three-carbon link. If there were a plane of symmetry between these two Hs, it would have to be the plane marked by the dashed yellow lines in the second diagram. This is *not* a plane of symmetry and the two Hs *are* diastereotopic. They have no neighbours, so they give a simple AB system. The coupling constant here is small for ²J—only 7 Hz—but that should not surprise you since we have a five-membered ring and a nearby oxygen atom.



The same principles apply to open-chain compounds, such as amino acids. All of the amino acids in proteins except glycine are chiral. Glycine has a prochiral CH₂ group that gives a singlet in the NMR spectrum as the Hs are enantiotopic. Similarly, the *N*-benzyl derivative of glycine has a second prochiral CH₂ group (NCH₂Ph) that gives another singlet in the NMR spectrum as these Hs too are enantiotopic.



The plane of the paper is a plane of symmetry for both these CH₂ groups in the way they are drawn here. The *N*-benzyl derivatives of the other amino acids are quite different. Each shows an AB signal for the NCH₂Ph group because these molecules have stereogenic centres and there are no planes of symmetry. The Hs of the NCH₂Ph group are diastereotopic.



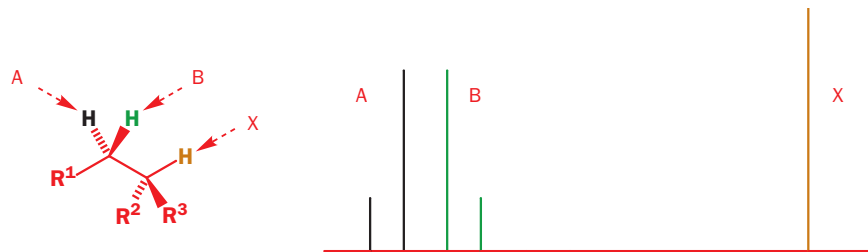
In the way in which the molecule is drawn, the brown H is on the same side as the Me group and the yellow H on the other. It does not matter that there is free rotation in this molecule—there is no conformation you can draw in which the important plane, passing between the diastereotopic Hs through their carbon atom, is a plane of symmetry.



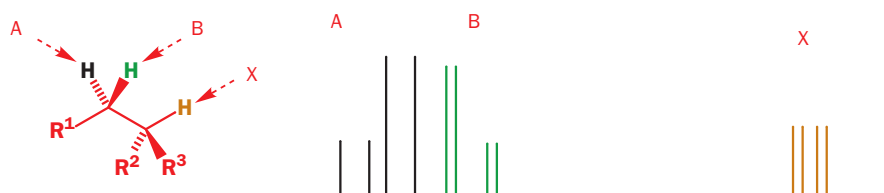
See p. 271 for the use of A, B, X, etc. to describe protons.

The ABX system

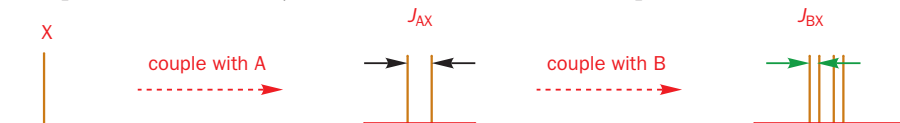
It is more common to find diastereotopic CH₂ groups with neighbours, and the most common situation is that in which there is one neighbour, giving an ABX system. We will outline diagrammatically what we expect. Let's start with the AB system for the diastereotopic CH₂ group and the singlet for the neighbour, which we call 'X' because it's at a quite different chemical shift.



Now we must add the coupling between A and X and between B and X. Since A and B are different, there is no reason why J_{AX} and J_{BX} should be the same. One is normally larger than the other, and both are normally smaller than J_{AB} , since J_{AX} and J_{BX} are vicinal ³ J couplings while J_{AB} is a geminal ² J coupling. We shall arbitrarily put $J_{AX} > J_{BX}$ in this example.

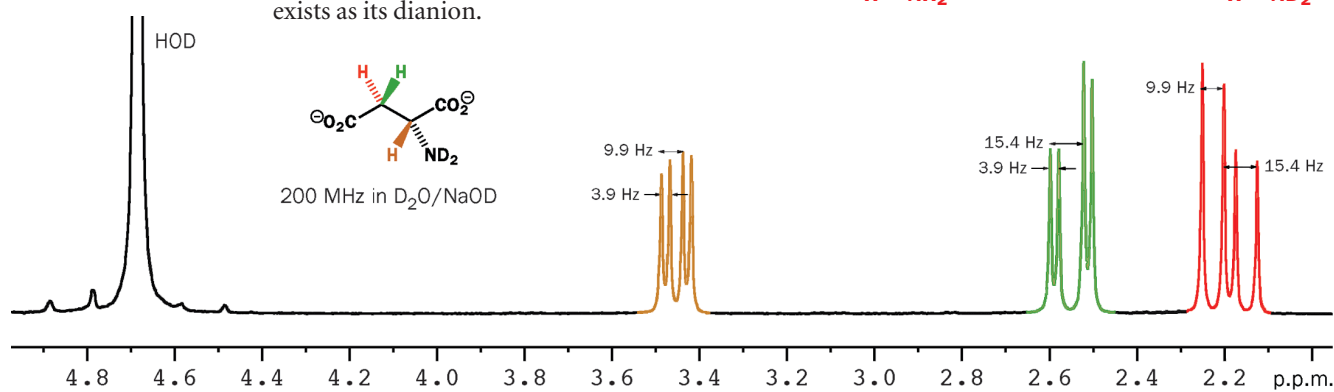


You can read J_{AX} and J_{BX} from the AB part of the signal quite easily by measuring the distance between each pair of lines, in Hz. If you want to read them from the X part, remember that it is made up like this.



In the signal for X, the larger coupling, J_{AX} , is the spacing between lines 1 and 3 or between lines 2 and 4 while the smaller coupling, J_{BX} , is the spacing between lines 1 and 2 or 3 and 4. Naturally, J_{AX} and J_{BX} are the same whether you measure them in the AB signal or in the X signal.

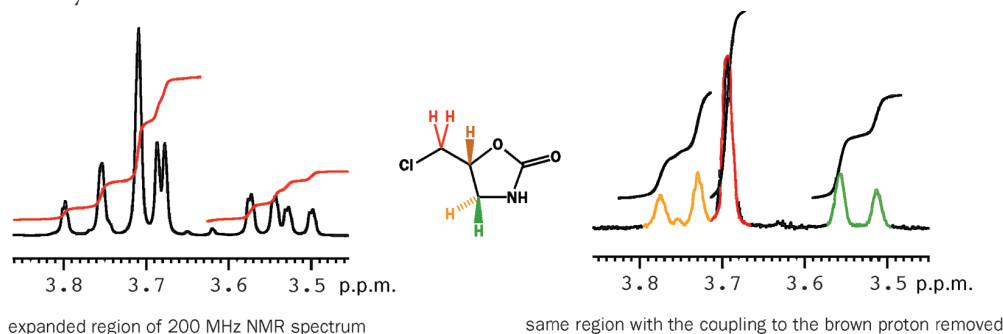
When aspartic acid is dissolved in D₂O with NaOD present, all OH and NH₂ protons are exchanged for deuterium atoms and do not show up in the spectrum—the molecule exists as its dianion.



The spectrum consists of a beautiful ABX system with the brown proton as a double doublet at δ_H 3.45 p.p.m. and the black and green protons as an AB pair between 2 and 3 p.p.m. The coupling between red and green is typical: 15 Hz.

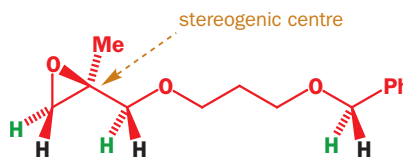
More complex examples

We have stressed all along that diastereotopic CH₂ groups may be separated in the proton NMR but need not be. It may just happen that the chemical shift difference is zero giving an A₂ system. It is not possible to predict which diastereotopic CH₂ groups will be revealed in the NMR spectrum as AB systems and which as A₂. Both may even appear in the same molecule. As an example, consider the compound shown below. The brown hydrogen has a very complicated signal, coupling to four other hydrogens. The spectrum for these four hydrogens is also complicated but may be simplified by irradiating the brown hydrogen to remove any coupling to it. Then we can clearly see that one CH₂ group shows itself as diastereotopic while the other does not. From the chemical shifts we may guess that the CH₂Cl group is the A₂X system at 3.7 p.p.m. and that it is the one in the ring that gives the ABX system.



As a general guide, CH₂ groups close to a stereogenic centre are more likely to be revealed as diastereotopic than those further away. Those in part of a structure with a fixed conformation are more likely to be revealed as diastereotopic than those in a flexible, freely rotating part of the molecule.

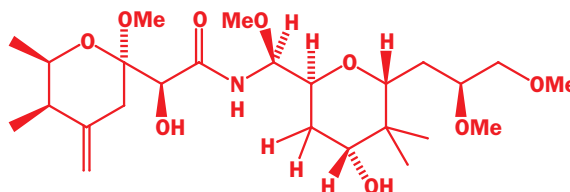
In this molecule, all three marked CH₂ groups are diastereotopic, but it is more likely that the ones next to the stereogenic centre, whether in the ring or in the open chain, will show up as AB systems in the NMR. The remote CH₂ group at the end of the chain is more likely to be A₂ in the NMR, but one cannot be sure. You must be able to recognize diastereotopic CH₂ groups and to interpret AB and ABX systems in the NMR. You must also not be surprised when a diastereotopic CH₂ group appears in the NMR spectrum as an A₂ or A₂X system.



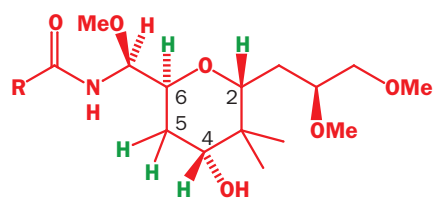
For another example, look back at thienamycin on p. 832. Compare the two OCH₂Ph groups: both have a diastereotopic CH₂ pair, but one appears as a singlet and one as an AB system.

Geminal coupling in six-membered rings

While we were discussing coupling in rings earlier in the chapter we avoided the question of geminal coupling by never considering the CH₂ groups in the ring. In practice there will often be diastereotopic CH₂ groups in six-membered rings. As an example, we will look at a problem in structure determination of a rather complex molecule. It is pederin, the toxic principle of the blister beetle *Paederus fuscipes*. After some incorrect early suggestions, the actual structure of the compound was eventually deduced.

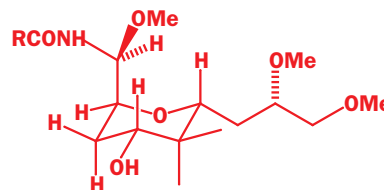


We are not going to discuss the full structure elucidation, but will concentrate on the stereochemistry of the right-hand ring. You can see that there is a CH₂ group in this ring and it has, of course, diastereotopic Hs. At first the OH group was placed at the wrong position on the ring, but a careful analysis of the NMR spectrum put this right and also gave the stereochemistry. The five (green) protons on the ring gave these signals (left-hand part of the molecule omitted for clarity).



δ_{H} 1.85 (1H, ddd, J 5, 10, 12)
2.10 (1H, ddd, J 3, 4, 12)
3.75 (1H, dd, J 4, 10)
3.85 (1H, ddd, J 3, 5, 8)
4.00 (1H dd, J 3, 7)

Three of the protons have shifts δ_{H} 3–4 p.p.m. and are obviously on carbons attached to oxygen atoms. The other two, δ_{H} about 2 p.p.m., must be the diastereotopic pair at C5. The coupling of 12 Hz, which appears in both signals, must be the geminal coupling and the other couplings are found in the signals at δ_{H} 3.75 and 3.85 p.p.m. The signal at δ_{H} 3.75 p.p.m. has no other couplings and must be from C4 so that leaves δ_{H} 3.85 p.p.m. for the hydrogen atom at C6 which is also coupled to the hydrogen in the side chain. The 10 Hz coupling is axial/axial but the others are all much smaller so we can draw the conformation immediately.



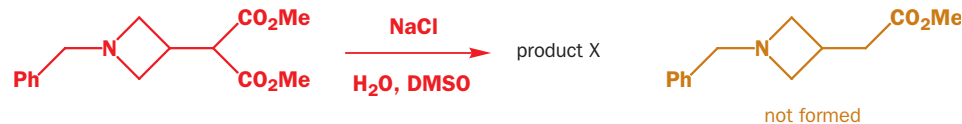
There is just the one axial/axial coupling and so the left-hand side chain must occupy an axial position. This is perhaps a bit surprising—it's large and branched—but the molecule has no choice but to place one of the two side chains axial.

A surprising reaction product

Chapter 26 revealed that sodium chloride can be a surprisingly powerful reagent. It removes ester groups from malonate derivatives, like this.

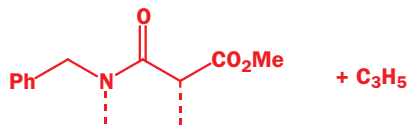


However, using this reaction to decarboxylate the malonate shown here did not merely remove the CO_2Me group. Instead, a compound was formed with a much more complicated NMR spectrum than that of the expected product (which was known as it could be made another way). The NMR data for both compounds are detailed below.



product X	product X	product X
$\text{C}_{14}\text{H}_{15}\text{NO}_3$	$\text{C}_{14}\text{H}_{15}\text{NO}_3$	$\text{C}_{13}\text{H}_{17}\text{NO}_2$
δ_{H} 7.35–7.25 (3H, m)	δ_{C} 169.1	δ_{H} 7.2–7.4 (5H, m, Ph)
7.2 (2H, d, J 7)	169.0	3.65 (3H, s, OMe)
4.45 (1H, d, J 14)	136.2	3.45 (2H, t, J 7)
4.3 (1H, d, J 14)	128.6	2.95–2.85 (2H, m)
3.8 (3H, s, OMe)	128.1	2.85–2.75 (1H, m)
3.45 (1H, dd, J 7, 10)	127.6	2.6 (2H, t, J 7)
3.1 (1H, d, J 10)	52.4	
2.35–2.25 (1H, m)	46.45	
1.9 (1H, dd, J 5, 10)	46.4	
1.1 (1H, t, J 5)	31.5	
	22.8	
	20.7	

The unknown product has lost MeOH but retained both carbonyl groups (δ_C 169.1, 169.0 p.p.m. typical for acid derivatives). In the ^1H NMR, the phenyl ring and one OMe group are still there. The other striking thing about the ^1H NMR is the presence of so many couplings. It looks as if all the hydrogens are magnetically distinct. Indeed we can see one diastereotopic CH_2 at 4.45 and 4.3 p.p.m. with $^2J = 14$ Hz. This is the ‘normal’ value and would fit well for the NCH_2Ph group. But note the chemical shift! For δ_H to be so large the nitrogen atom must be part of an amide, which would also explain the two acid derivative $\text{C}=\text{O}$ groups. So we have the partial structure on the right.



All that is left is C_3H_5 and this must be fitted in where the dotted lines go. One reasonable interpretation from the NMR would be two diastereotopic CH_2 groups, one with $^2J = 10$ and one with $^2J = 5$ Hz, linked by a CH group.

If this is the case, what has brought the values of 2J down from 14 to 10 and even 5 Hz? Electronegative elements can't be the culprits as the only one is nitrogen, but small rings could. If, in fact, we simply join these two fragments together in rather a surprising way (the dotted lines show how), we get the correct structure.

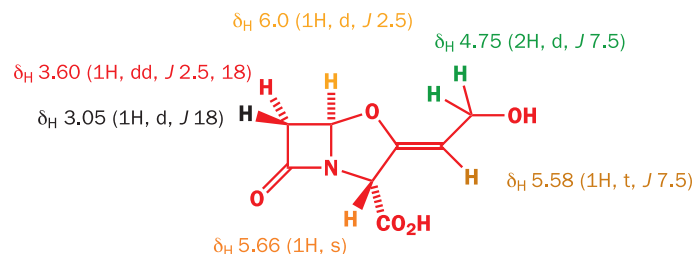


In this case, the geminal couplings do not help to assign the stereochemistry—the three- and five-membered rings can only be fused *cis* (just try making a model of the *trans* compound!)—but they do help in assigning the structure.

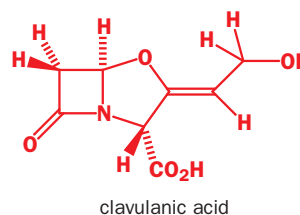
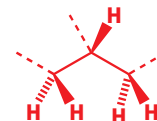
We should at this point just recap what we have done here—we made no attempt to work out the structure by thinking about what the mechanism of the reaction might be. We used, purely and simply, NMR to work out fragments of the structure which we then put together in a logical way. Considering reasonable mechanisms can be a help in structure determination—but it can also be a hindrance. If the product is unexpected, it follows that the mechanism is unexpected too.

For an example with a four-membered ring, we go back to β -lactams. A serious problem with β -lactam antibiotics is that bacteria develop resistance by evolving enzymes called β -lactamases, which break open the four-membered ring. In 1984, a team from Beechams reported the exciting discovery of some very simple inhibitors of these enzymes all based on the core structure named clavulanic acid. This too was a β -lactam but a much simpler one than the penicillins we saw earlier.

The structure elucidation used all the usual spectroscopic techniques as well as X-ray crystallography, but it is the ^1H NMR that is particularly interesting to us here. Here it is, with the assignments shown.



Notice the very large geminal coupling between the red and the black hydrogens (more of this later) and the fact that the green hydrogens, though actually diastereotopic, resonate at the same chemical shift. The *cis* coupling across the four-membered ring is larger (2.5 Hz) than the *trans* coupling (0 Hz) as expected.



The π contribution to geminal coupling

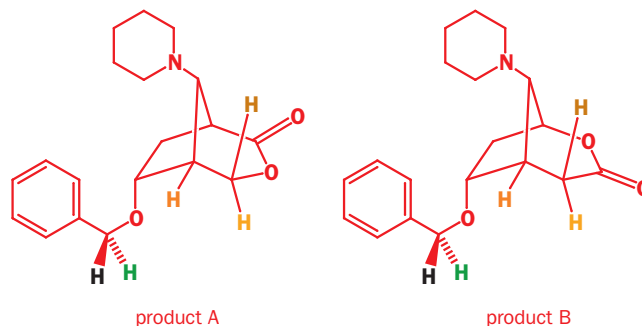
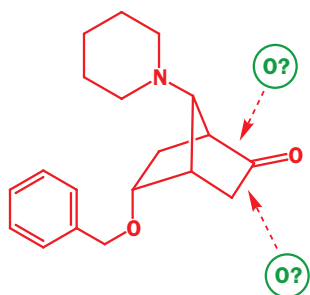
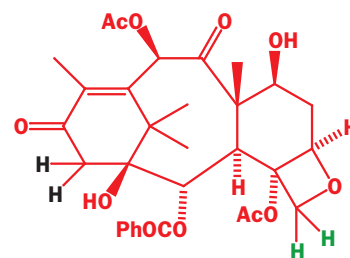
We began this chapter with a diagram of Taxol. This molecule is rather too complex for us to analyse in detail, but the geminal couplings of an important closely related compound are worth noting. Here are the details.

The coupling between the black Hs is 20 Hz while that between the green Hs is 6 Hz. This is a rather extreme example as the green Hs are in a four-membered ring and next to an oxygen atom, so they are expected to show a small J value, while the black Hs are in a six-membered ring and not next to an electronegative element. Nevertheless, 20 Hz is a very large coupling constant. The reason is the adjacent π bond. If a CH_2 group is next to an alkene, aromatic ring, $\text{C}=\text{O}$ group, CN group, or any other π -bonded functional group, it will have a larger geminal coupling constant. This effect is quite clear in both Taxol and clavulanic acid.

The oxidation of the bicyclic amino-ketone shown in the margin demonstrates how useful this effect can be. This is the Baeyer–Villiger rearrangement, which you will meet in Chapter 37. The mechanism is not important here: all you need to know is that it inserts an oxygen atom on one side or the other of the ketone $\text{C}=\text{O}$ group. The question is—which side?

In fact, both lactones were isolated and the problem then became—which was which? In both NMR spectra there were AB systems at 4.6–4.7 for diastereotopic CH_2 groups isolated from the rest of the molecule, with $^2J = 11.8$ Hz. These are clearly the black and green hydrogens on the benzyl groups. The coupling constant is reduced by the oxygen atom and increased by the phenyl's π contribution, so it ends up about average.

Both lactones also had clear ABX systems in the NMR corresponding to the yellow, brown, and orange protons. In one compound $^2J = 10.8$ Hz and in the other $^2J = 18.7$ Hz. The smaller value has been reduced by neighbouring oxygen and this must be compound A. The larger value has been increased by the π contribution from the carbonyl group and this must be compound B.



● The size of 2J and 3J coupling constants

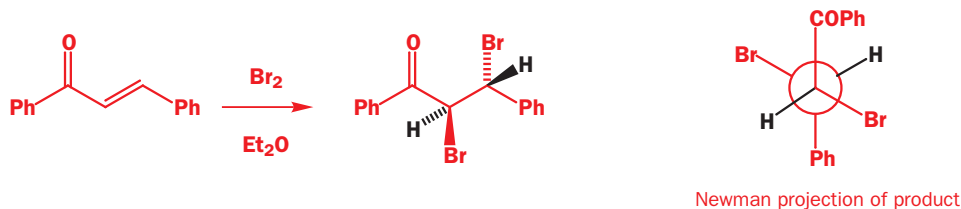
We have now covered all of the important influences on the size of coupling constants. They are:

- dihedral angle: 3J greatest at 180° and 0° ; about 0 Hz at 90°
- ring size, which leads to 'spreading out' of bonds and lower 2J and lower 3J in small rings
- electronegative atoms, which decrease 2J and 3J coupling constants between protons
- π systems, which increase 2J coupling constants between protons

The nuclear Overhauser effect

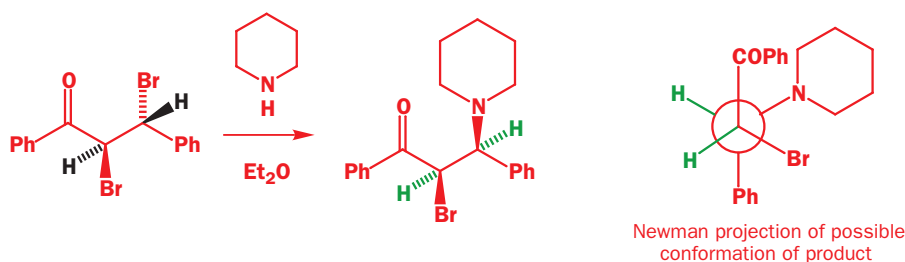
Many occasions arise when even coupling constants do not help us in our quest for stereochemical information. Consider this simple sequence. Bromination of the alkene gives as expected *trans* addition and a single diastereoisomer of the dibromide.

■ We looked at the stereoselectivity of electrophilic additions to double bonds in Chapter 20.

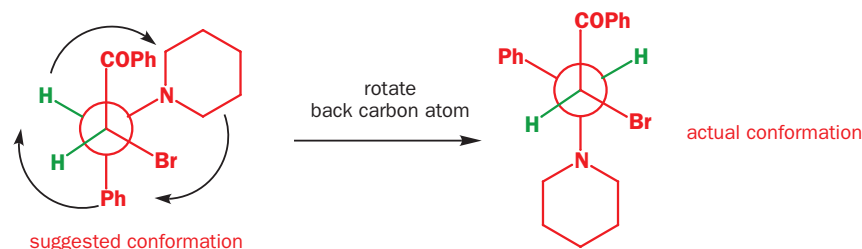


The vicinal (3J) coupling constant between the two black Hs is 11 Hz. This is rather large and can be explained by a predominant conformation shown in the Newman projection, with the two large groups (PhCO and Ph) as far from each other as possible, the two medium groups (Br) as distant as possible, and the two black Hs in the places which are left. The dihedral angle between the black Hs is then 180° (they are anti-periplanar) and a large J is reasonable.

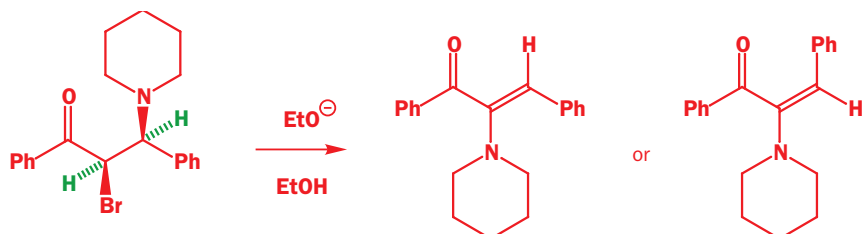
But now see what happens when we react the dibromide with piperidine. A single diastereoisomer of an amine is formed, and there is good evidence that it has the opposite configuration from the dibromide; in other words, replacement of Br by N has occurred with inversion.



We might expect that the conformation would now be different and that, since inversion has occurred, the two green Hs would now be gauche instead of anti-periplanar. With a dihedral angle of 60° the coupling constant would be much less. But it isn't. The coupling constant between the green Hs is exactly the same (11 Hz) as the coupling constant between the black Hs in the starting material. Why? The new substituent (piperidine) is very big, much bigger than Br and probably bigger in three dimensions than a flat Ph group. The conformation must change (all we are doing is rotating the back carbon atom by 120°) so that the two green Hs also have a dihedral angle of 180° .



A more serious situation arises when we treat this product with base. An unusual elimination product is formed, in which the amine group has moved next to the ketone. The reaction is interesting for this point alone, and one of the problems at the end of the chapter asks you to suggest a mechanism. But there is added interest, because the product is also formed as a single geometrical isomer, *E* or *Z*. But which one? There is a hydrogen atom at one end of the alkene but not at the other so we can't use 3J coupling constants to find out as there aren't any.



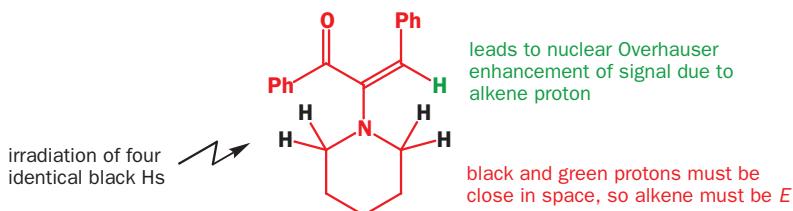
What we need is a method that allows us to tell which groups are close to one another in space (though not necessarily through bonds) even when there are no coupling constants to help out. Very fortunately, an effect in NMR known as the **nuclear Overhauser effect** allows us to do this.

The details of the origin of the nuclear Overhauser effect are beyond the scope of this book, but we can give you a general idea of what the effect is. As you learned from Chapter 11, when a proton NMR spectrum is acquired, a pulse of radiofrequency electromagnetic radiation jolts the spins of the protons in the molecule into a higher energy state. The signal we observe is generated by those spins dropping back to their original states. In Chapter 11 it sufficed to assume that the drop back down was spontaneous, just like a rock falling off a cliff. In fact it isn't—something needs to 'help' the protons to drop back again—a process called **relaxation**. And that 'something' is other nearby magnetically active nuclei—usually more protons. Notice *nearby*—nearby in space not through bonds. With protons, relaxation is fast, and the number of nearby protons does not affect the appearance of the NMR spectrum.

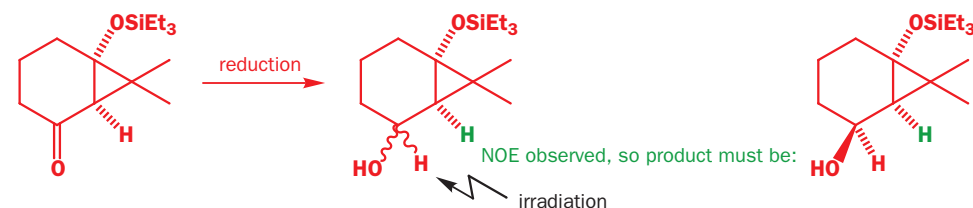
We find that, although peak intensity is independent of the number of nearby protons, by using methods whose description is beyond the scope of this book, it is possible to make the intensity respond, to a small extent, to those protons that are nearby. The idea is that as certain protons (or groups of identical protons) are irradiated selectively (in other words, they are jolted into their high-energy state and held there by a pulse of radiation at exactly the right frequency—not the broad pulse needed in a normal NMR experiment). Under the conditions of the experiment, this causes protons that *were* relying on the irradiated protons to relax them to appear as a slightly more intense (up to a few per cent) peak in the NMR spectrum. This effect is known as the nuclear Overhauser effect, and the increase in intensity of the peak the nuclear Overhauser enhancement. Both are shortened to 'NOE'.

All you need to be aware of at this stage is that irradiating protons in an NOE experiment gives rise to enhancements at other protons that are nearby in space—no coupling is required, and NOE is *not* a through-bond phenomenon. The effect also drops off very rapidly: the degree of enhancement is proportional to $1/r^6$ (where r is the distance between the protons) so moving two protons twice as far apart decreases the enhancement one can give to the other by a factor of 64. NOE spectra are usually presented as differences: the enhanced spectrum minus the unenhanced, so that those protons that change in intensity can be spotted immediately.

Applying NOE to the problem in hand solves the structure. If the protons next to the nitrogen atom in the piperidine ring are irradiated, the signal for the alkene proton increases in intensity, so these two groups of protons must be near in space. The compound is the *E*-alkene.



Data from NOE experiments nicely supplement information from coupling constants in the determination of three-dimensional stereochemistry too. Reduction of this bicyclic ketone with a bulky hydride reducing agent gives one diastereoisomer of the alcohol, but which? Irradiation of the proton next to the OH group leads to an NOE to the green proton.

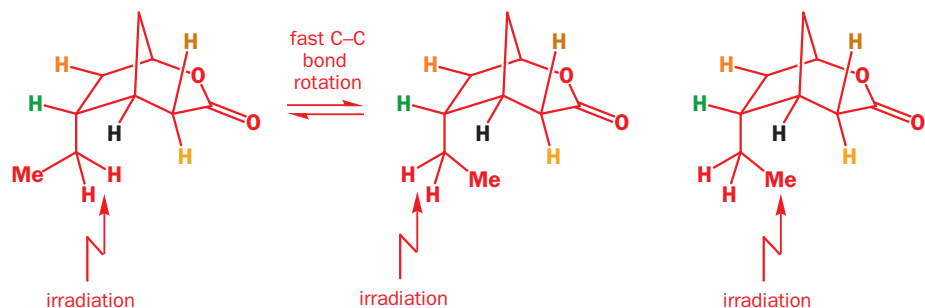
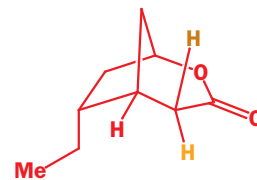


This suggests that the two protons are on the same side of the molecule and that reduction has occurred by hydride delivery to the face of the ketone opposite the two methyl groups on the three-membered ring.

► Why you can't integrate ^{13}C NMR spectra

Relaxation is the real reason why you can't integrate ^{13}C signals. Relaxation of ^{13}C is slow, but is fastest with lots of nearby protons. This is the reason that you will often find that $-\text{CH}_3$ groups show strong signals in the ^{13}C NMR, while quaternary carbons, with no attached protons, show weak ones: quaternary carbons relax only slowly, so we don't detect such an intense peak. Allowing plenty of time for all ^{13}C atoms to relax between pulses gives more proportionally sized peaks, but at the expense of a very long NMR acquisition time.

For a more complex example we can return to a lactone (shown in the margin) obtained by oxidation of a bicyclic ketone similar to the one we mentioned earlier (p. 844). When this compound was made, two questions arose. What was the stereochemistry of the ethyl group, and which signal in the NMR spectrum belonged to which hydrogen atom? In particular, was it possible to distinguish the signals of the diastereotopic brown and yellow Hs? Three experiments were carried out, summarized in the diagrams below. First the CH₂ and then the CH₃ protons of the ethyl group were irradiated and the other protons were observed. Finally, the green proton was irradiated.



In the first experiment, enhancement of the signals of the black, yellow, and green Hs was observed. The ethyl group can rotate rapidly on the NMR time-scale so all the enhancements can be explained by the first two conformations. An NOE effect to the yellow but not to the brown H is particularly significant. Irradiation of the methyl group led to enhancement of the yellow proton but not the brown. Clearly, the ethyl group is in the position shown.

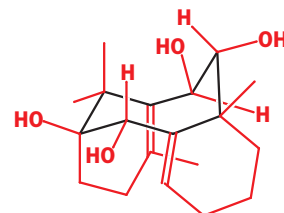
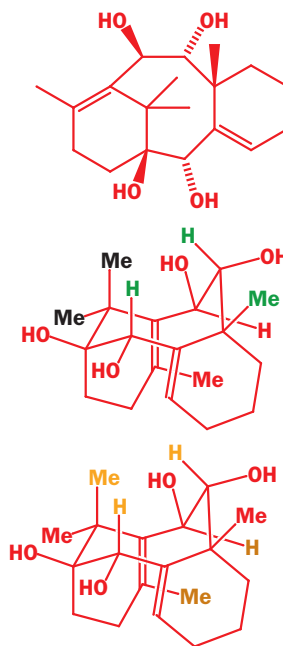
Irradiation of the green proton, whose stereochemistry is now clear, enhanced the orange proton and allowed its chemical shift to be determined. Previously, it had been lost in the many CHs in the rings.

We shall finish this chapter by returning to Taxol once more. The tricyclic compound drawn here was made in 1996 as an intermediate for Taxol synthesis. The stereochemistry and the conformation of the molecule were deduced by a series of NOE experiments.

Four NOE experiments were carried out, summarized two at a time in the diagrams on the right. Irradiation of the methyl groups established that the black pair were on the same carbon atom and hence allowed assignment of the spectrum. Then irradiation of the remaining methyl group on saturated carbon established the proximity of the green hydrogens and gave the stereochemistry at three centres.

Next irradiation of the brown methyl group on a double bond showed it was close to the brown hydrogen and gave the stereochemistry at that centre. Finally, irradiation at one of the two methyl groups of the CMe₂ group (yellow) showed that it was close to the two green hydrogens and hence all these three groups were clustered in the centre of the molecule. It's important here to draw a conformational diagram as they do not look very close in the flat diagram shown.

These experiments fixed not only the stereochemistry at all the stereogenic centres but also allowed the conformation of the central eight-membered ring to be deduced. This ring is outlined in black on the diagram in the margin and has two chair-like sections. It is no trivial matter to work out such conformations without X-ray data and the NOE result tells us about the more important conformation *in solution*, rather than in the crystal. The alliance between coupling constants and NOE gives us a powerful method for structural determination.



To conclude...

As you leave this chapter, you should carry the message that, while X-ray crystallography is the ‘final appeal’ with regard to determining configuration, NMR can be a very powerful tool too. Analysis of coupling constants and nuclear Overhauser effects allows:

- determination of configuration, even in noncrystalline compounds
- determination of conformation in solution

As you embark on the next two chapters, which describe how to make molecules stereoselectively, bear in mind that many of the stereochemical outcomes were deduced using the techniques we have described in this chapter.

Problems

Note. All NMR shifts are in p.p.m. and coupling constants are quoted in hertz (Hz). The usual abbreviations are used: d = doublet; t = triplet; and q = quartet.

1. A revision problem to start you off easily. A Pacific sponge contains 2.8% dry weight of a sweet-smelling oil with the following spectroscopic details. What is its structure and stereochemistry?

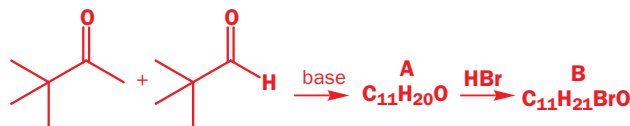
Mass spectrum gives formula: $C_9H_{15}O$

IR 1680, 1635 cm^{-1}

δ_H 0.90 (6H, d, J 7), 1.00 (3H, t, J 7), 1.77 (1H, m), 2.09 (2H, t, J 7), 2.49 (2H, q, J 7), 5.99 (1H, d, J 16), and 6.71 (1H, dt, J 16, 7)

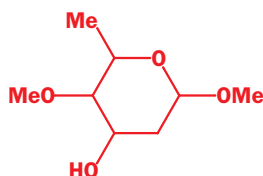
δ_C 8.15 (q), 22.5 (two qs), 28.3 (d), 33.1 (t), 42.0 (t), 131.8 (d), 144.9 (d), and 191.6 (s)

2. Reaction between this aldehyde and ketone in base gives a compound A with the 1H NMR spectrum: δ 1.10 (9H, s), 1.17 (9H, s), 6.4 (1H, d, J 15) and 7.0 (1H, d, J 15). What is its structure? (Don't forget stereochemistry!) When this compound reacts with HBr it gives compound B with this NMR spectrum: δ 1.08 (9H, s), 1.13 (9H, s), 2.71 (1H, dd, J 1.9, 17.7), 3.25 (dd, J 10.0, 17.7), and 4.38 (1H, dd, J 1.9, 10.0). Suggest a structure, assign the spectrum, and give a mechanism for the formation of B.

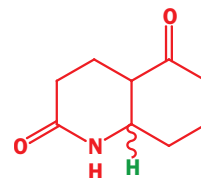


3. One of the sugar components in the antibiotic kijanimycin has the gross structure and NMR spectrum shown below. What is its stereochemistry? All couplings in Hz; signals marked * exchange with D_2O .

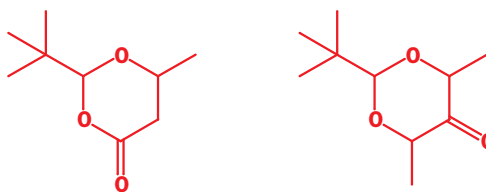
δ_H 1.33 (3H, d, J 6), 1.61* (1H, broad s), 1.87 (1H, ddd, J 14, 3, 3.5), 2.21 (1H, ddd, J 14, 3, 1.5), 2.87 (1H, dd, J 10, 3), 3.40 (3H, s), 3.47 (3H, s), 3.99 (1H, dq, J 10, 6), 4.24 (1H, ddd, J 3, 3, 3.5), and 4.79 (1H, dd, J 3.5, 1.5)



4. Two diastereoisomers of this cyclic keto-lactam have been prepared. The NMR spectra have many overlapping signals but the proton marked in green can clearly be seen. In isomer A it is δ_H 4.12 (1H, q, J 3.5), and isomer B has δ_H 3.30 (1H, dt, J 4, 11, 11). Which isomer has which stereochemistry?



5. How would you determine the stereochemistry of these two compounds?

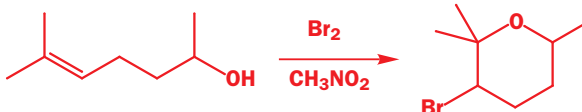


6. The structure and stereochemistry of the anti-fungal antibiotic ambruticin was in part deduced from the NMR spectrum of this simple cyclopropane. Interpret the NMR spectrum and show how it gives definite evidence on the stereochemistry.

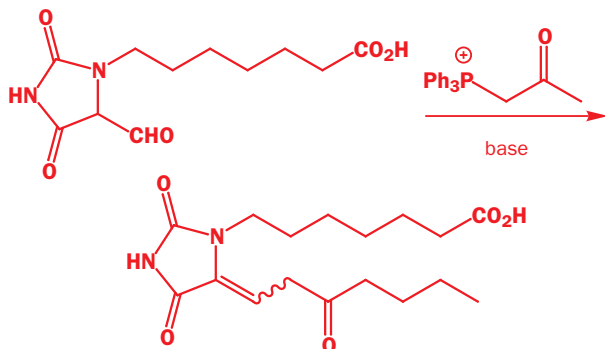


δ_H 1.21 (3H, d, J 7 Hz), 1.29 (3H, t, J 9), 1.60 (1H, t, J 6), 1.77 (1H, ddq, J 6, 13, 7), 2.16 (1H, dt, J 6, 13), 4.18 (2H, q, J 9), 6.05 (1H, d, J 20), and 6.62 (1H, dd, J 13, 20).

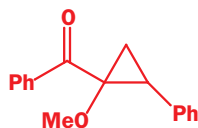
7. In Chapter 20 we set a problem asking you what the stereochemistry of a product was. Now we can give you the NMR spectrum of the product and ask: how do we know the stereochemistry of the product? You need only the partial NMR spectrum: δ_H 3.9 (1H, ddq, J 12, 4, 7) and 4.3 (1H, dd, J 11, 3).



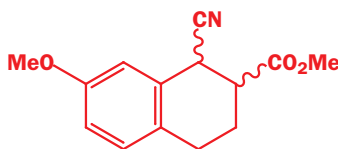
8. The structure of a Wittig product intended as a prostaglandin model was established by the usual methods—except for the geometry of the double bond. Irradiation of a signal at 3.54 (2H, t, J 7.5) led to an enhancement of another signal at δ_{H} 5.72 (1H, t, J 7.1) but not to a signal at δ_{H} 3.93 (2H, d, J 7.1). What is the stereochemistry of the alkene? How is the product formed?



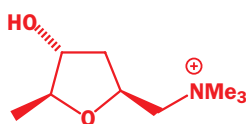
9. How would you determine the stereochemistry of this cyclopropane? The NMR spectra of the three protons on the ring are given: δ_{H} 1.64 (1H, dd, J 6, 8), 2.07 (1H, dd, J 6, 10), and 2.89 (1H, dd, J 10, 8).



10. A chemical reaction produces two diastereoisomers of the product. Isomer A has δ_{H} 3.08 (1H, dt, J 4, 9, 9) and 4.32 (1H, d, J 9) while isomer B has δ_{H} 4.27 (1H, d, J 4). The other protons overlap. Isomer B is converted into isomer A on treatment with base. What is the stereochemistry of A and B?

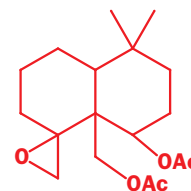


11. Muscarine, the poisonous principle of the death cap mushroom, has the following structure and proton NMR spectrum. Assign the spectrum. Can you see definite evidence for the stereochemistry? All couplings in Hz; signals marked * exchange with D_2O .



δ_{H} 1.16 (3H, d, J 6.5), 1.86 (1H, ddd, J 12.5, 9.5, 5.5), 2.02 (1H, ddd, J 12.5, 2.0, 6.0), 3.36 (9H, s), 3.54 (1H, dd, J 13, 9.0), 3.74 (1H, dd, J 13, 1.0), 3.92 (1H, dq, J 2.5, 6.5), 4.03 (1H, m), 4.30* (1H, d, J 3.5), and 4.68 (1H, m).

12. An antifeedant compound that deters insects from eating food crops has the gross structure shown below. Some of the NMR signals that can clearly be made out are also given. Since NMR coupling constants are clearly useless in assigning the stereochemistry, how would you set about it?



δ_{H} 2.22 (1H, d, J 4), 2.99 (1H, dd, J 4, 2.4), 4.36 (1H, d, J 12.3), 4.70 (1H, dd, J 4.7, 11.7), 4.88 (1H, d, J 12.3)

13. The seeds of the Costa Rican plant *Ateleia herbert smithii* are avoided by all seed eaters (except a weevil that adapts them for its defence) because they contain two toxic amino acids (IR spectra like other amino acids). Neither compound is chiral. What is the structure of these compounds? They can easily be separated because one (A) is soluble in aqueous base but the other (B) is not.

A is $\text{C}_6\text{H}_9\text{NO}_4$ (mass spectrum) and has δ_{C} 34.0 (d), 40.0 (t), 56.2 (s), 184.8 (s), and 186.0 (s). Its proton NMR has three exchanging protons on nitrogen and one on oxygen and two complex signals at δ_{H} 2.68 (4H, A_2B_2 part of $\text{A}_2\text{B}_2\text{X}$ system) and 3.37 (X part of $\text{A}_2\text{B}_2\text{X}$ system) with J_{AB} 9.5, J_{AX} 9.1, and J_{BX} small.

B is $\text{C}_6\text{H}_9\text{NO}_2$ (mass spectrum) and has δ_{C} 38.0 (d), 41.3 (t), 50.4 (t), 75.2 (s), and 173.0 (s). Its proton NMR spectrum contains two exchanging protons on nitrogen and δ_{H} 1.17 (2H, ddd, J 2.3, 6.2, 9.5), 2.31 (2H, broad m), 2.90 (1H, broad t, J 3.2), and 3.40 (2H, broad s).

Because the coupling pattern did not show up clearly as many of the coupling constants are small, decoupling experiments were used. Irradiation at δ_{H} 3.4 simplifies the δ_{H} 2.3 signal to (2H, ddd, J 5.8, 3.2, 2.3), sharpens each line of the ddd at 1.17, and sharpens the triplet at 2.9.

Irradiation at 2.9 sharpens the signals at 1.17 and 2.9 and makes the signal at 2.31 into a broad doublet, J about 6. Irradiation at 2.31 sharpens the signal at 3.4 slightly and reduces the signals at 2.9 and 1.17 to broad singlets. Irradiation at 1.17 sharpens the signal at 3.4 slightly so that it is a broad doublet, J about 1.0, sharpens the signal at 2.9 to a triplet, and sharpens up the signal at 2.31 but irradiation here had the least effect.

This is quite a difficult problem but the compounds are so small (C_6 only), have no methyl groups, and have some symmetry so you should try drawing structures at an early stage.

