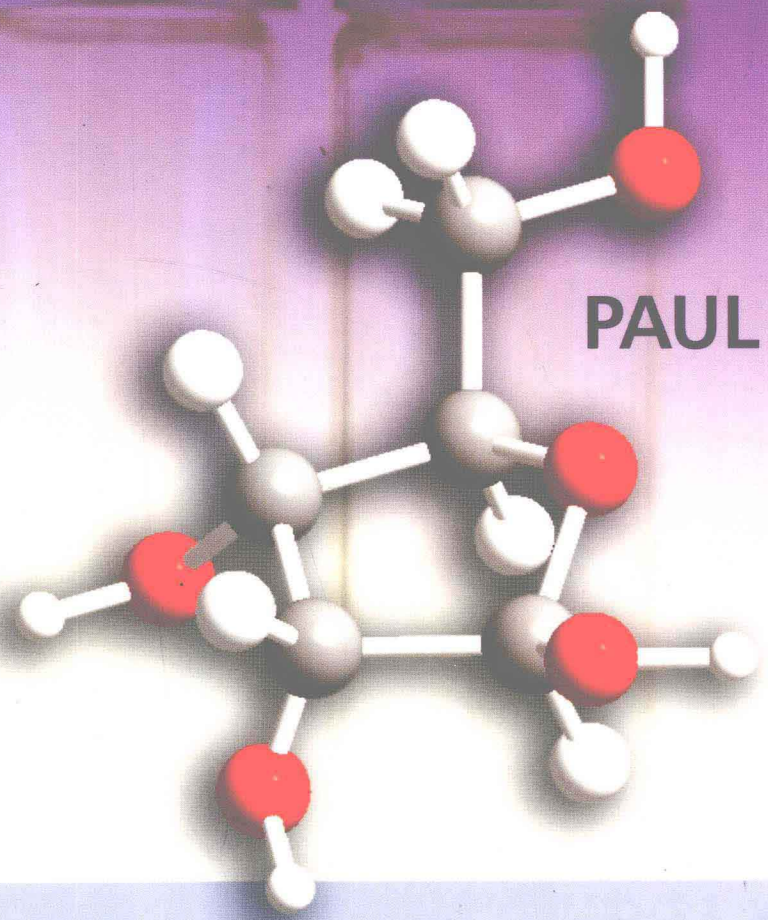
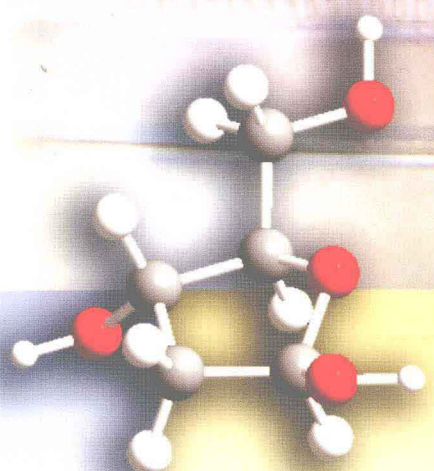
Essentials of Organic Chemistry

For Students of Pharmacy, Medicinal Chemistry and Biological Chemistry



PAUL M DEWICK



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For students of pharmacy, medicinal chemistry and biological chemistry

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Preface

For more years than I care to remember, I have been teaching the new intake of students to the Nottingham pharmacy course, instructing them in those elements of basic organic chemistry necessary for their future studies. During that time, I have also referred them to various organic chemistry textbooks for additional reading. These texts, excellent though they are, contain far too much material that is of no immediate use to pharmacy students, yet they fail to develop sufficiently areas of biological and medicinal interest we would wish to study in more detail. The organic chemistry needs of pharmacy students are not the same as the needs of chemistry students, and the textbooks available have been specially written for the latter group. What I really wanted was an organic chemistry textbook, considerably smaller than the 1000–1500-page tomes that seem the norm, which had been designed for the requirements of pharmacy students. Such a book would also serve the needs of those students on chemistry-based courses, but who are not specializing in chemistry, e.g. students taking medicinal chemistry and biological chemistry. I have wanted to write such a book for a long time now, and this is the result of my endeavours. I hope it proves as useful as I intended it.

Whilst the content is not in any way unique, the selection of topics and their application to biological systems should make the book quite different from others available, and of especial value to the intended readership. It is a combination of carefully chosen material designed to provide a thorough grounding in fundamental chemical principles, but presenting only material most relevant to the target group and omitting that which is outside their requirements. How these principles and concepts are relevant to the study of pharmaceutical and biochemical molecules is then illustrated through a wide range of examples.

I have assumed that readers will have some knowledge of organic chemistry and are familiar with the basic philosophy of bonding and reactivity as covered in pre-university courses. The book then presents material appropriate for the first 2 years of a university pharmacy course, and also provides the fundamental chemical groundwork for courses in medicinal chemistry, biological chemistry, etc. Through selectivity, I have generated a textbook of more modest size, whilst still providing a sufficiently detailed treatment for those topics that are included.

I have adopted a mechanism-based layout for the majority of the book, an approach that best enables the level of detail and selection of topics to be restricted in line with requirements. There is a strong emphasis on understanding and predicting chemical reactivity, rather than developing synthetic methodology. With extensive use of pharmaceutical and biochemical examples, it has been possible to show that the same simple chemistry can be applied to real-life complex molecules. Many of these examples are in self-contained boxes, so that the main theme need not be interrupted. Lots of cross-referencing is included to establish links and similarities; these do not mean you have to look elsewhere to understand the current material, but they are used to stress that we have seen this concept before, or that other uses are coming along in due course.

I have endeavoured to provide a friendly informal approach in the text, with a clear layout and easy-to-find sections. Reaction schemes are annotated to keep material together and reduce the need for textual explanations. Where alternative rationalizations exist,

I have chosen to use only the simpler explanation to keep the reasoning as straightforward as possible. Throughout, I have tried to convince the reader that, by applying principles and deductive reasoning, we can reduce to a minimal level the amount of material that needs be committed to memory. Worked problems showing typical examination questions and how to approach them are used to encourage this way of thinking.

Four chapters towards the end of the book diverge from the other mechanism-oriented chapters. They have a strong biochemical theme and will undoubtedly overlap with what may be taught separately by biochemists. These topics are approached here from a chemical viewpoint, using the same structural and mechanistic principles developed earlier, and should provide an alternative perspective. It is probable that some of the material described will not be required during the first 2 years of study, but it could sow the seeds for more detailed work later in the course.

There is a measure of intended repetition; the same material may appear in more than one place. This is an important ploy to stress that we might want to look at a particular aspect from more than one viewpoint. I have also used similar molecules in different chapters as illustrations of chemical structure or reactivity. Again, this is an intentional strategy to illustrate the multiple facets of real-life complex molecules.

I am particularly grateful to some of my colleagues at Nottingham (Barrie Kellam, Cristina De Matteis, Nick Shaw) for their comments and opinions. I would also like to record the unknowing contribution made by Nottingham pharmacy students over the years. It is from their questions, problems and difficulties that I have shaped this book. I hope future generations of students may benefit from it.

Finally, a word of advice to students, advice that has been offered by organic chemistry teachers many times previously. *Organic chemistry is not learnt by reading*: paper and pencil are essential at all times. It is only through drawing structures and mechanisms that true understanding is attained.

Paul M Dewick
Nottingham, 2005

Contents

1

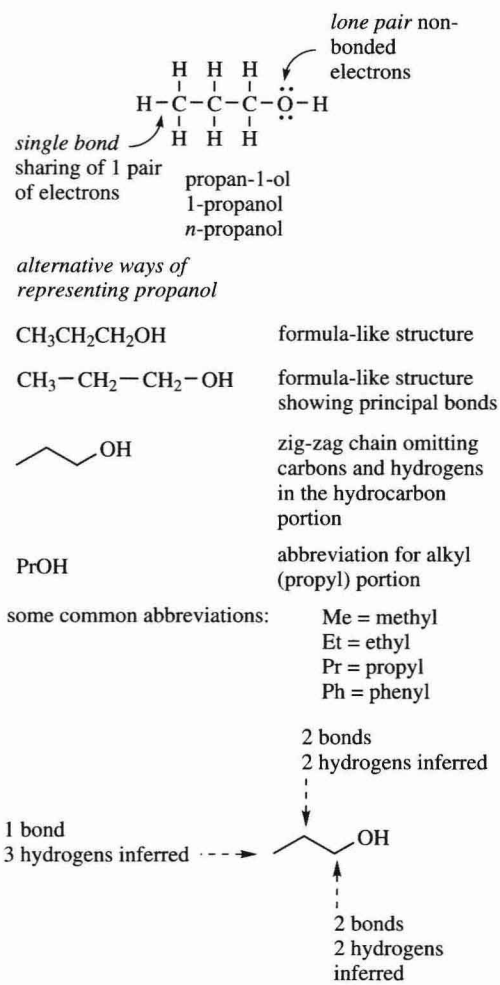
Molecular representations and nomenclature

1.1 Molecular representations

From the beginnings of chemistry, scientists have devised means of representing the materials they are discussing, and have gradually developed a comprehensive range of shorthand notations. These cover the elements themselves, bonding between atoms, the arrangement of atoms in molecules, and, of course, a systematic way of naming compounds that is accepted and understood throughout the scientific world.

The study of carbon compounds provides us with the subdivision 'organic chemistry', and a few simple organic compounds can exemplify this shorthand approach to molecular representations. The primary alcohol propanol (systematically propan-1-ol or 1-propanol, formerly *n*-propanol, *n* signifying normal or unbranched) can be represented by a structure showing all atoms, bonds, and lone pair or non-bonding electrons.

Lines are used to show what we call **single bonds**, indicating the sharing of one pair of electrons. In writing structures, we have to remember the number of bonds that can be made to a particular atom, i.e. the **valency** of the atom. In most structures, carbon is tetravalent, nitrogen trivalent, oxygen divalent, and hydrogen and halogens are univalent. These valencies arise from the number of electrons available for bonding. More often, we trim this type of representation to one that shows the layout of the carbon skeleton with attached hydrogens or other atoms. This can be a formula-like structure without



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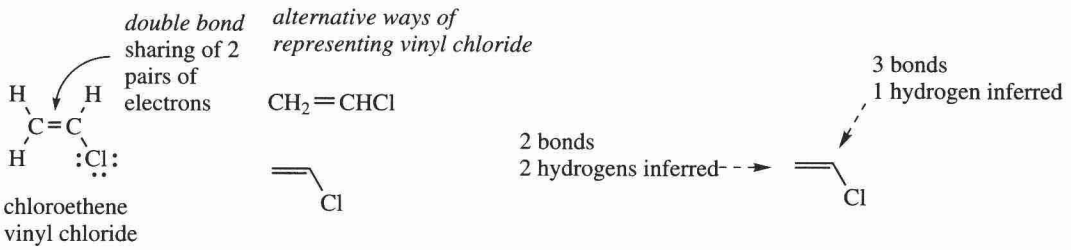
bonds, or it can be one showing just the principal bonds, those of the carbon chain.

However, for many complex structures, even these approaches become too tedious, and we usually resort to a shorthand version that omits most, if not all, of the carbon and hydrogen atoms. Propanol is now shown as a **zig-zag chain** with an OH group at one end. The other end of the chain, where it stops, is understood to represent a methyl group; three attached hydrogens have to be inferred. At a point on the chain, two hydrogens are assumed, because two bonds to carbons are already shown. In a structure where three bonds joined, a single additional hydrogen would be assumed (see vinyl chloride, below).

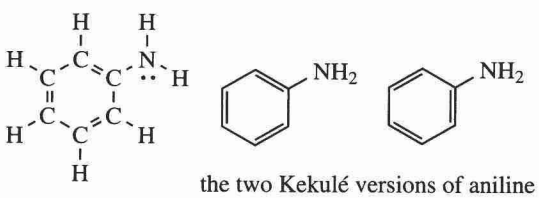
The zig-zag arrangement is convenient so that we see where carbons are located (a long straight line would not tell us how many carbons there are), but it also mimics the low-energy arrangement (conformation) for such a compound (see Section 3.3.1). Note that it is usual to write out the hydroxyl, or some alternative group, in full. This group, the so-called **functional group**, tends to be the reactive part of the molecule that we shall be considering in reactions. When we want an even more concise method of writing the molecule, abbreviations for an alkyl (or aryl) group may be used, in which case propanol becomes PrOH. Some more common abbreviations are given later in Table 1.3.

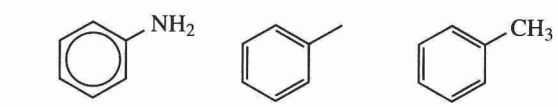


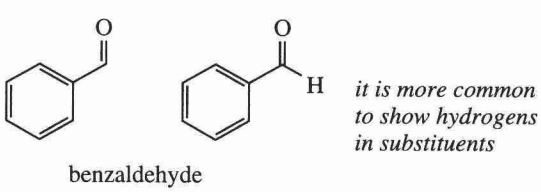
Double bonds, representing the sharing of two pairs of electrons, are inferred by writing a double line. Vinyl chloride (systematically chloroethene) is shown as two different representations according to the conventions we have just seen for propanol. Note that it is customary always to show the reactive double bond, so that CH_2CHCl would not be encountered as an abbreviation for vinyl chloride.

The six-membered cyclic system in **aromatic rings** is usually drawn with alternating double and single bonds, i.e. the **Kekulé form**, and it is usually immaterial which of the two possible versions is used. Aniline (systematically aminobenzene or benzenamine) is shown with and without carbons and hydrogens. It is quite rare to put in any of the ring hydrogens on an aromatic ring, though it is sometimes convenient to put some in on the substituent, e.g. on a methyl, as in toluene (methylbenzene), or an aldehyde group, as in benzaldehyde.

Benzene strictly does not have alternating double and single bonds, but the aromatic sextet of electrons is localized in a π orbital system and bond lengths are somewhere in between double and single bonds

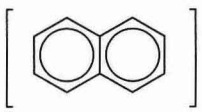






(see Section 2.9.4). To represent this, a circle may be drawn within the hexagon. Unfortunately, this version of benzene becomes quite useless when we start to draw reaction mechanisms, and most people continue to draw benzene rings in the Kekulé form. In some cases, such as fused rings, it is actually incorrect to show the circles.

two Kekulé versions of naphthalene

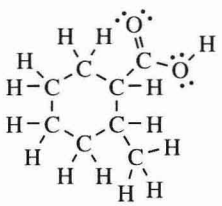


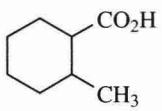
each circle must represent six aromatic π electrons

this is strictly incorrect!

Thus, naphthalene has only 10 π electrons, one from each carbon, whereas the incorrect two-circle version suggests it has 12 π electrons.

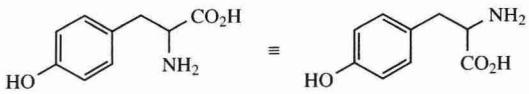
We find that, in the early stages, students are usually happier to put in all the atoms when drawing structures, following earlier practices. However, you are urged to adopt the shorthand representations as soon as possible. This saves time and cleans up the structures of larger molecules. Even a relatively simple molecule such as 2-methylcyclohexanecarboxylic acid, a cyclohexane ring carrying two substituents, looks a mess when all the atoms are put in. By contrast, the line drawing looks neat and tidy, and takes much less time to draw.





2-methylcyclohexanecarboxylic acid

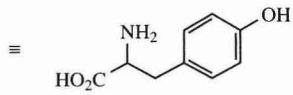
Do appreciate that there is no strict convention for how you orientate the structure on paper. In fact, we will turn structures around, as appropriate, to suit our needs. For example, the amino acid tyrosine has three functional groups, i.e. a carboxylic acid, a primary amine, and a phenol. How we draw tyrosine will depend upon what modifications we might be considering, and which functional group is being altered.



tyrosine

we might use this version if we were considering reactions of the carboxylic acid group

we might use this version if we were considering reactions of the amine group



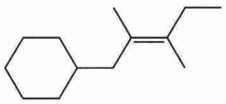
we might use this version if we were considering reactions of the phenol group

You will need to be able to reorientate structures without making mistakes, and also to be able to recognize different versions of the same thing. A simple example is with esters, where students have learnt that ethyl acetate (ethyl ethanoate) can be abbreviated to $CH_3CO_2C_2H_5$. When written backwards, i.e. $C_2H_5OCOCH_3$, the ester functionality often seems less recognizable.

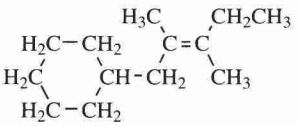
1.2 Partial structures

We have just seen that we can save a lot of time and effort by drawing structures without showing all of the atoms. When we come to draw reaction sequences, we shall find that we are having to repeat large chunks of the structure each time, even though no chemical changes are occurring in that part of the molecule. This is unproductive, so we often end up writing down just that part of the structure that is of interest, i.e. a **partial structure**. This will not cause problems when you do it, but it might when you see one and wish to interpret it.

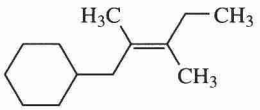
In the representations overleaf, you can see the line drawing and the version with methyls that stresses the bond ends. Both are satisfactory. When we wish to consider the reactivity of the double bond, and perhaps want to show that reaction occurs irrespective of the alkyl groups attached to the double bond, we put in the abbreviation R (see below), or usually just omit them. When we omit the attached groups, it helps to show what we mean by using wavy lines across the bonds, but in our urge to proceed we tend to omit even these indicators. This may



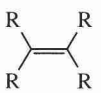
a typical line drawing



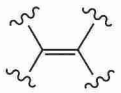
this is what the line drawing conveys



this version emphasizes the chain ends



using the R abbreviation for an unspecified alkyl group; different R groups may be indicated by R^1, R^2, R^3, etc., or R, R', R'', etc.



a partial structure; this shows the double bond that has four groups attached; wavy lines indicate bonds to something else

in context, this might mean the same, but could be mistaken for a double bond with four methyls attached

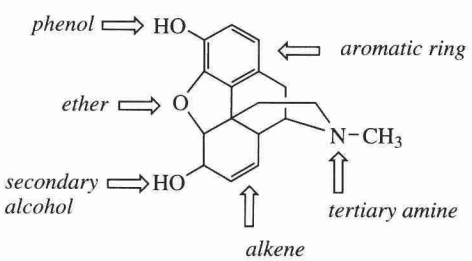
this would be better; putting in the carbons emphasizes that the other lines represent bonds, not methyls

cause confusion in that we now have what looks like a double bond with four methyls attached, not at all what we intended. A convenient ploy is to differentiate this from a line drawing by putting in the alkene carbons.

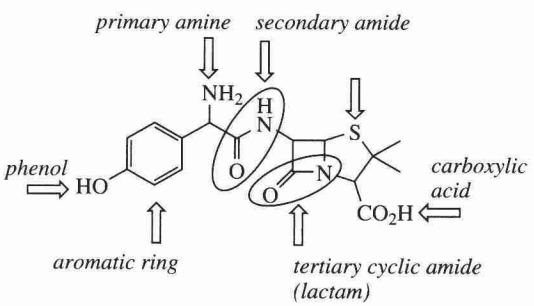
1.3 Functional groups

The reactivity of a molecule derives from its **functional group** or groups. In most instances the hydrocarbon part of the molecule is likely to be unreactive, and the reactivity of the functional group is largely independent of the nature of the hydrocarbon part. In general terms, then, we can regard a molecule as R–Y or Ar–Y, a combination of a functional group Y with an alkyl group R or aryl group Ar that is not participating in the reaction under consideration. This allows us to discuss reactivity in terms of functional groups, rather than the reactivity of individual compounds. Of course, most of the molecules of interest to us will have more than one functional group; it is this combination of functionalities that provides the reactions of chemical and biochemical importance. Most of the functional groups we shall encounter are included in Table 1.1, which also contains details for their nomenclature (see Section 1.4).

It is particularly important that when we look at the structure of a complex molecule we should visualize it in terms of the functional groups it contains. The properties and reactivity of the molecule can generally be interpreted in terms of these functional groups. It may sometimes be impossible to consider the reactions of each functional group in complete isolation, but it is valuable to disregard the complexity and perceive the simplicity of the structure. With a little practice, it should be possible to dissect the functional groups in complex structures such as morphine and amoxicillin.



morphine



amoxicillin