# Molecular structure and reactivity

ASSIGN BUSTER

Shape is a fundamentally important molecular feature that often determines the fate of a drug with respect to molecular interactions it will have with both its preferred and non-preferred biological targets. Complementarity of binding in small-molecule-protein, peptide-receptor, antigen-antibody and protein-protein interactions is the key to life, survival and the basis on which modern medicine is built. It is therefore imperative that any student of the life sciences or pharmacy has a thorough grasp of the concept of molecular shape. The following series of tasks are designed to give you an introduction into the relationships that exist between 2D representations of molecules, and how this relates to their 3D nature.

## 2D Representations of Molecular Structure

It is necessary to draw structural formulae for organic compounds because in most cases a molecular formula does not uniquely represent a single compound. Different compounds having the same molecular formula are called isomers, and the prevalence of isomers of organic compounds reflects the extraordinary versatility of carbon in forming strong bonds to itself and to other elements.

When the group of atoms that make up the molecules of different isomers are bonded together in fundamentally different ways, we refer to such compounds as constitutional isomers. For example, there are seven constitutional isomers of C4H10O, and structural formulas for these are drawn in the following table. These formulae represent all known and possible C4H10O compounds, and display a common structural feature. There are no double or triple bonds and no rings in any of these structures. Note that each of the carbon atoms is bonded to four other

atoms, and is saturated with its bonding partners i. e. there are no carbon-carbon double or triple bonds in any of these structures.

As can be seen from the table above, simplification of structural formulas may be achieved without any loss of the information they convey.
In condensed structural formulas the bonds to each carbon are omitted, but each distinct structural unit (group) is written with subscript numbers designating multiple substituents, including the hydrogens. Shorthand (line/skeletal) formulas omit the symbols for carbon and hydrogen entirely. Each straight line segment represents a bond, the ends and intersections of the lines are carbon atoms, and the correct number of hydrogens is calculated from the tetravalency of carbon. Developing the ability to visualize a three-dimensional structure from two-dimensional formulas requires practice, and in most cases the aid of molecular models.

## Exercise A

Task 1: In your groups use the molecular modelling kits provided to build the seven structural formulas given for C4H10O in the table above, to convince yourself of the structural differences between the constitutional isomers. Copy the shorthand notation for each of the isomers into the space below, and label the functional groups within the molecule.

Task 2: In your groups use the molecular modelling kits to construct all constitutional isomers with the molecular formula C6H14. In the space below give the shorthand and condensed formulae for each of the isomers. Give systematic names to each of the isomers you identify.

# Exercise B

The three dimensional shape or configuration of a molecule is an important characteristic. This shape is dependent on the preferred spatial orientation of covalent bonds to atoms having two or more bonding partners. Three dimensional configurations are best viewed with the aid of models. In order to represent such configurations on a two-dimensional surface (paper, blackboard or screen), we often use perspective drawings in which the direction of a bond is specified by the line connecting the bonded atoms. In most cases the focus of configuration is a carbon atom so the lines specifying bond directions will originate there. As defined in the diagram on the right, a simple straight line represents a bond lying approximately in the surface plane. The two bonds to substituents A in the structure on the left are of this kind. A wedge shaped bond is directed in front of this plane (thick end pointing toward the viewer), as shown by the bond to substituent B; and a hatched bond is directed in back of the plane (away from the viewer), as shown by the bond to substituent D.

Task 1: In your groups use the molecular modelling kits provided to build the molecules given below. Label the functional groups on the molecules below. What do you notice about the structure of these molecules? Are they superimposable?

The models ARE all superimposable.

This means that the same molecule has been drawn in 3 different ways

Each way is equally valid.

Task 2: Draw the following shorthand formulae as perspective drawings in the space below. If it helps, use the model kit to build models of the shorthand structures. None of the structures contain any ring structures or double or triple bonds. Label all the functional groups in your perspective models.

CH3NH2 B) HOCH2Cl C) CH3O(CH2)2CH3

D) BrC(CH3)3 E) CH3(CH2)3CH(Cl)2 F) C3H8

Task 3: Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used for relief of symptoms of arthritis, primary dysmenorrhoea, fever and as an analgesic where there is an inflammatory component. Label the functional groups on the shorthand structure given below and build a model of ibuprofen using the molecular modelling kits provided. Is your model the same as other members of your group? Can you superimpose the models you have made? Redraw the shorthand representation given below as a perspective structure. Which C atom will you choose as the central atom in the perspective structure? Why?

If the positions of the functional groups vary at the C atom marked with a * you can’t superimpose the molecules.

This is because the C marked with a * is a chiral carbon atom.

Therefore, you should use the chiral carbon atom as the central atom in a perspective structure.

3D-Perspective Drawing of Ibuprofen.

# Exercise C:

Cycloalkanes have one or more rings of carbon atoms. The simplest examples of this class consist of a single, unsubstituted carbon ring, and these form a homologous series similar to the unbranched alkanes. The IUPAC names of the first five members of this series are given in the following table. The last (yellow shaded) column gives the general formula for a cycloalkane of any size. If a simple unbranched alkane is converted to a cycloalkane two hydrogen atoms, one from each end of the chain must be lost. Hence the general formula for a cycloalkane composed of n carbons is CnH2n. Although a cycloalkane has two fewer hydrogens than the equivalent alkane, each carbon is bonded to four other atoms so such compounds are still considered to be saturated with hydrogen.

Task 1: In your groups, use your molecular modelling kits to build each of the cycloalkanes shown in the table above. Are any of them difficult to make? Why? Which ones are most flexible? Which cycloalkanes do you think have the highest C-C bond energies? Why?

3-membered and 4-membered rings most difficult to make. Large deviation of internal bond angles from ideal sp3 hybridisation angle of 109. 5o. The angle strain means that the C-C bonds in 3 and 4 membered rings are weak.

The larger rings – cyclohexane and cycloheptane are the most flexible.

Cyclohexane has the highest C-C bond energies. This is because all the carbon atoms in a cyclohexane ring are able to adopt C-C bond angles of 109. 5o. This means that there is no angle strain within the ring to weaken the C-C bonds.

Benzene (Figure 1) is an organic chemical compound with the molecular formula C6H6. Benzene is an aromatic hydrocarbon i. e. a cyclic hydrocarbon with a continuous p bond. This can be represented in shorthand form in 3 different ways 2 variations of using alternating double and single bonds within the six-membered ring or by drawing a circle within the ring to represent the delocalised p electrons. These are used interchangeably in most literature but all representations mean the same thing.

Task 2: In your groups, use the molecular modelling kits to construct models of benzene and cyclohexane. What are the differences between the two molecules?

Benzene is flat and rigid.

Cyclohexane not flat – puckered – also flexible – call this conformational mobility.

Bond angles between the carbon atoms are different – 109. 5o in cyclohexane (sp3 hybridised C atoms) and 120o in benzene (sp2 hybridised C atoms)

The nomenclature of substituted benzene ring compounds is less systematic than that of the alkanes, alkenes and alkynes. A few mono-substituted compounds are named by using a group name as a prefix to “ benzene”, as shown by the combined names listed below. The majority of these compounds, however, are referred to by singular names that are unique. There is no simple alternative to memorization in mastering these names.

Examples of Combined Names

Examples of Singular Names

When more than one substituent is present on a benzene ring, the relative locations of the substituents must be designated by numbering the ring carbons or by some other notation. In the case of disubstituted benzenes, the prefixes ortho (o-), meta (m-) & para (p-) are commonly used to indicate a 1, 2- or 1, 3- or 1, 4- relationship respectively. Examples are given below.

If there are three or more substituent groups, the ring is numbered in such a way as to assign the substituents the lowest possible numbers, as illustrated by the last row of examples. The substituents are listed alphabetically in the final name. If the substitution is symmetrical (third example from the left) the numbering corresponds to the alphabetical order.

Task 3: Draw shorthand structures for the following di- and tri-substituted benzenes. Clearly label the functional groups on each structure. Can you give each structure another valid name? (look at diagram for disubstituted benzenes given above for guidance).

2-methylphenol B) p-aminophenol C) 1, 3, 5-trinitrotoluene

D) meta-chloroanisole E) 4-methylaniline F) 3-bromobenzonitrile

G) p-chlorostyrene H)3-fluorobromobenzene I) m-aminophenol

Task 4: Resorcinol, salicylic acid, xylene and benzocaine, are the singular names given to four disubstituted benzenes. Use the resources available to you in the laboratory to identify the shorthand structures for these compounds and draw them below. Give alternative names for each of the

compounds. What are the clinical applications of benzocaine and resorcinol? Do you think the relative arrangement of functional groups on the benzene ring is important for the therapeutic activity of resorcinol and benzocaine? What would happen if the relative position of the functional groups on the benzene ring changed?

Shape is important for conferring therapeutic properties of a drug molecule.

Alteration in the positions of the relative positions of the functional groups on the molecule will change the shape of the molecule.

This may lead to the molecule losing its therapeutic ability.

This is due to the fact that the mechanism of drug action is based on a lock and key principle. Altering the position of the functional groups in a molecule will change the shape of the key.