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Chemistry NOW

This is a series of four leaflets which present modern aspects of chemistry in a way accessible to school students and directly usable by teachers. Each leaflet consists of four pages of information interspersed with questions to test student's understanding of what they are reading, to help them to link what they have read to the chemistry they already know and to help them to understand the text.

The leaflets could be used to support existing workschemes, to develop comprehension skills or as meaningful exercises to be used in the case of teacher absences (planned or unplanned).

The leaflets are:

•Chemistry and sport

This is aimed at 14–16 year olds and deals with the chemistry of aerobic and anaerboic respiration in the context of athletics and looks at a number of ways in which athletes can manipulate (legally!) the chemistry of this process to their advantage by monitoring the concentration of lactic acid in their blood.

•Chemistry of the atmosphere

This is aimed at 14–16 year olds. This looks at the way that the Earth's present atmosphere has evolved from possible earlier atmospheres. Some of the available evidence for different scenarios is presented and critically discussed.

•Computational chemistry

This is aimed at the post-16 age group. It presents a case study of the development of derivatives of cinnamic acid as a repellent to dissuade birds from eating crops treated with it. It explains how chemists develop relationships between structural features and particular types of activity and how computer modelling programmes are used in this work.

•Combinatorial chemistry

This is also aimed at the post-16 age group. Combinatorial chemistry is a group of techniques for synthesising large arrays of related chemicals. These can be easily automated by the use of robot syringes controlled by computers to carry out repetitive processes. The resulting arrays of chemicals called 'libraries' can then be screened for potential drug activities. Combinatorial chemistry is increasingly being used by pharmaceutical companies in their search for new drugs.

Electron distribution of cinnamamide

Answers

For the use of teachers, answers to the questions on the leaflets are presented overleaf.

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Computational chemistry

Computers have become essential tools for chemists, as they have for people in most walks of life. As well as standard uses such as word processing, spreadsheets, databases, searching the Internet and e-mail, many chemists use molecular modelling programmes to predict a wide range of properties of molecules before they have even been made. This is an enormous help to chemists who are looking for new compounds which they hope will have some activity as medicines, herbicides, pesticides *etc.* Molecular modelling gives chemists a good idea of whether a compound is likely to be useful before they begin making it in the laboratory and testing it in real life. Perhaps more importantly, they can discard less-promising compounds without having to go to the trouble and expense of synthesising them. Of course computer programmes cannot directly predict (yet!) a property such as 'the ability to repel pigeons from cereal seeds' or an 'antidepressant effect', but they can predict chemical and physical properties which might have a bearing on these sorts of effect.

A comment by a senior chemist at a company which makes agrochemicals helps to explain the potential of molecular modelling. He believes that in the forseeable future it will be possible to predict the concentration of a decomposition product of an agrochemical (such as a herbicide or pesticide) in a particular river at a particular time after applying it, before the substance has even been made! This point has not been reached yet, but the following account of the discovery of a compound which does repel pigeons from cereal seeds helps to explain how molecular modelling assists chemists.

•The first observation

The story starts with a report from a fruit grower that bullfinches were devastating his crop by eating the buds off pear trees. However, the buds of another variety in a nearby orchard were left untouched. The report was confirmed by observations in the field, and the search began to find the cause.

The cause was assumed to be chemical, and a team of chemists extracted and separated the chemicals in the two varieties of pears to look for differences. Eventually the compound cinnamic acid (*trans*-3-phenylprop-2-enoic acid) was suspected. It was tested by offering pigeons a choice of seeds treated with cinnamic acid and untreated seeds. The birds took significantly less of the treated seeds (Box 1).

TESTING REPELLENT ACTIVITY — Box 1

Cinnamic acid (and derivatives) was tested for its effect on pigeons, quail and rats in the laboratory and against various birds in the field. One type of test was the 'no choice trial'. In this test birds were offered untreated seed and the mass of it they normally ate was established by weighing the amount of it taken per day.

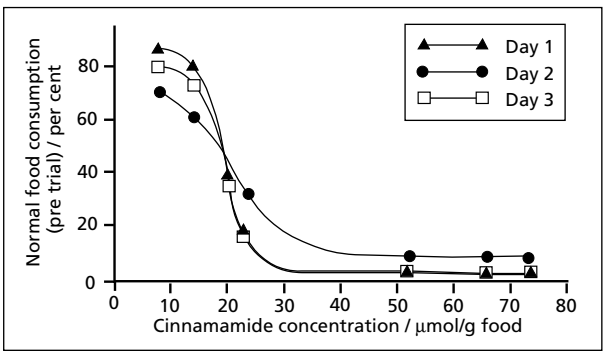
On the days of the trial, only food treated with a particular concentration of the chemical under test was made available, and the mass of this which was eaten was found. On other days, the concentration of chemical used to treat the food was increased.

The results obtained for the compound cinnamamide (a derivative of cinnamic acid) are shown in the top graph.

These results suggest that the repellent effect increases with concentration up to about 30 μmol/g of food after which there is no further increase.

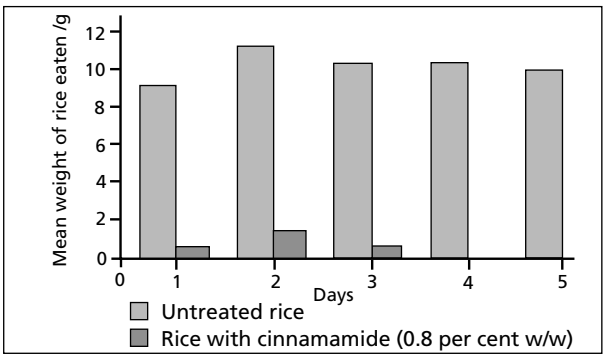
In a 'two choice test', the birds were offered a choice of both treated and untreated seeds and the masses of each which were taken were measured. Typical results (for cinnamamide) are shown in the bottom graph.

Both types of test indicate that birds are repelled by cinnamamide.



Above: The repellancy of cinnamamide to feral pigeons: a dose response curve

Below: The effect of cinnamamide on the consumption of rice by the chestnut-capped blackbird: two choice test



Structure-activity relationships

The trials proved that cinnamic acid (and some of its derivatives) does have some bird-repelling effect. But how does it work? What property (or properties) of the molecule causes the effect – shape, size, acidity, charge distribution *etc*? Could a more effective compound be found? This is an example of a common situation for chemists in the pharmaceutical and agrochemical industries. The normal procedure is to synthesise many compounds related to the 'lead compound' (in this case cinnamic acid), test their effectiveness and ultimately produce what is called a quantitative structure-activity relationship (QSAR). This is a link between some property of the molecules – shape, size, acidity, charge distribution *etc* – and how effective they are.

Experimental data about effectiveness are obtained for many compounds, and computers are used to relate this to a variety of different properties until the chemist can build up a picture of which properties are relevant and how these are linked to the desired effect – *eg* bird repellency. The set of compounds tested is called a learning series.

Molecular modelling

Now chemical computer modelling can help. Once the properties which are relevant have been identified from the experimental data, computer modelling programmes can calculate the relevant properties for other derivatives of the lead compound which have never been made. The likely effectiveness of a variety of these 'virtual compounds' can be predicted. Only the ones predicted to have potential are made in the laboratory for actual testing.

Types of modelling programme

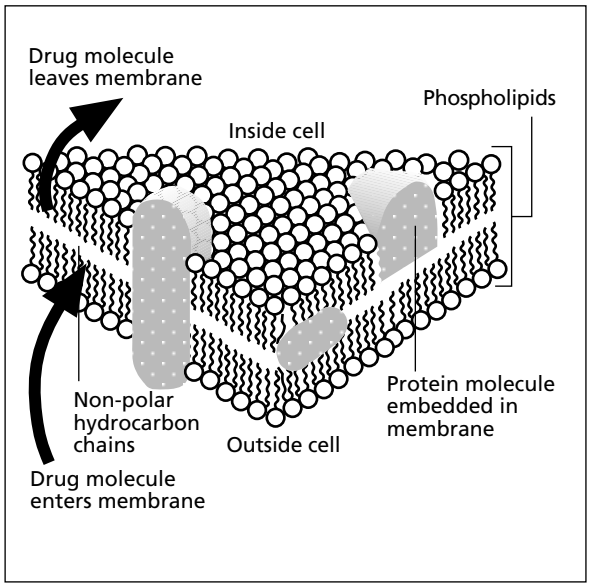
You may have come across a simple molecular graphics programme such as "Chem-3D"®. The formula of a substance is entered and the programme 'knows' enough chemistry to calculate the 3-dimensional shape of the molecule. It 'knows' for example that the H-C-H angle in a saturated hydrocarbon chain is 109.5° and that the C–H bond length is 0.109 nm.

However, bond lengths and angles do not completely define the shape of a molecule except in very simple cases. Single bonds can rotate, and this rotation means that there are many different shapes which a molecule can adopt. These are called conformations. You can explore the conformations that the compound cinnamamide can adopt by making a ball and stick model of it (using *Fig 2(a)* as a guide).

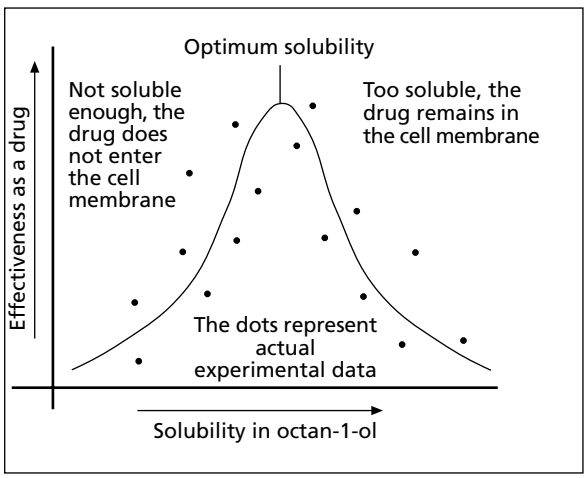
LIPOPHILICITY **Box 2**

It is sometimes difficult to see how a particular property (or properties) might have a bearing on a chemical's ability to have a biological effect. The lipophilicity (solubility in non-polar solvents) of a medicine is one example.

To work as a medicine, a compound must be able to pass through the cell membrane. Cell membranes are made of phospholipids - molecules with long hydrocarbon chains - and are therefore essentially non-polar. To pass into the cell membrane from the blood stream, a molecule must be relatively non-polar. However, if it is to pass out of the membrane again and into the cell (which is aqueous), it must not be too non-polar or it will stay in the cell membrane.



The polarity of the compound octan-1-ol is almost exactly the same as that of the cell membrane, so the solubility in octan-1-ol is one important predictor of how effective a compound might be as a medicine. Too insoluble and it is unable to get into the cell because it does not dissolve in the membrane at all, too soluble and it is retained in the membrane and not released into the cell.



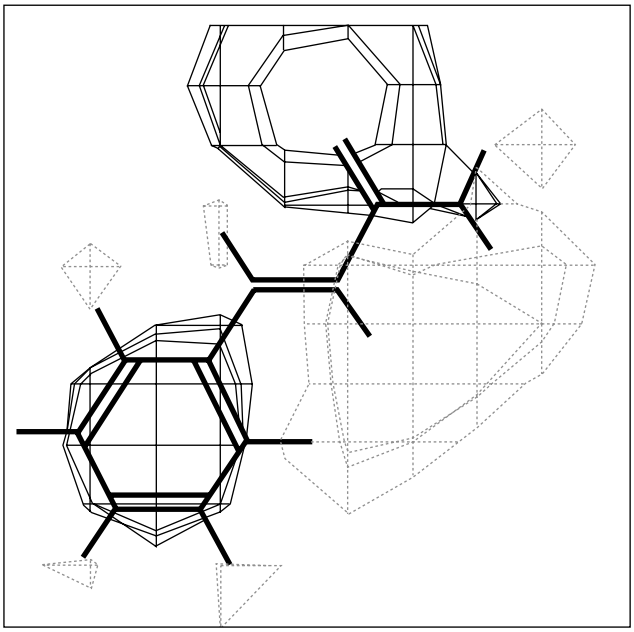


Fig. 1
The narrow lines represent the electron distribution around the cinnamamide molecule. The grey areas are $\delta+$ and the black lines are $\delta-$

Modelling programmes can calculate the energy of different conformations. The actual shape a molecule adopts will be the lowest energy conformation.

Molecular mechanics programmes calculate energies of different conformations by treating the molecule as a series of balls of known mass (the atoms) held together by springs of known stiffness (the bonds), just like a ball and spring molecular model. They can calculate the energies of different shapes from these mechanical properties. For example, the programme 'knows' that stretching a spring from its natural length increases its energy, as does compressing a spring. The principle of this method is for the computer to take a particular conformation and calculate its energy. It then makes a small change and calculates the energy again and so on. The most stable conformation, the one the molecule actually adopts, is the one with lowest energy.

This type of model cannot calculate electronic properties such as polarity or electron distribution.

Quantum mechanics programmes are more complex. The most sophisticated (called *ab initio*, meaning 'from the beginning') calculate properties by solving the Schrödinger equation – an equation derived from a theory called quantum mechanics which fully describes any molecule. Solving this equation exactly is possible only for very simple molecules. So, 'semi-empirical' quantum mechanical models are used. These use relationships derived from experimental measurements (this is what 'empirical' means) as well, to 'help out' the calculations. However, the principle is the same as for molecular mechanics, the programme makes many small changes to the molecule's properties and calculates the energy of each variant. The molecule actually adopts the variant which has the lowest energy. *Ab initio* programmes require a lot of computing power, but semi-empirical modelling can be done even on standard desktop PCs provided the molecules are relatively simple.

As well as molecular shape, quantum mechanical programmes can calculate properties such as size, solubility in different solvents, acidity, electron distribution (how $\delta+$ and $\delta-$ areas are placed) and many more. Usually there are several properties of a molecule which correlate with the desired effect. In bird repellency of derivatives of cinnamic acid, the electron distribution of the molecule was found to be most important (*Fig 1*).

For the bird repellent, experimental data were obtained for 20 properties of 18 derivatives of cinnamic acid which were then tested in field trials. Cinnamic acid is an unusual case in that it is a fairly simple molecule; many derivatives were already available off-the-shelf from chemical suppliers, and relatively few had to made. Molecular modelling provided predicted data for five more compounds.

A simple derivative of cinnamic acid, cinnamamide (*Fig 2*) proved to be an effective bird repellent. In fact it was one of the compounds actually used experimentally to establish the structure-activity relationship rather than one of those modelled. It is now undergoing the tests required before such a compound can be sold. These include tests on toxicity towards humans, other mammals, fish and insects; its effect on plants; and experiments to establish what happens to it in the environment – is it washed into rivers, how does it decompose, how toxic are its decomposition products *etc*?

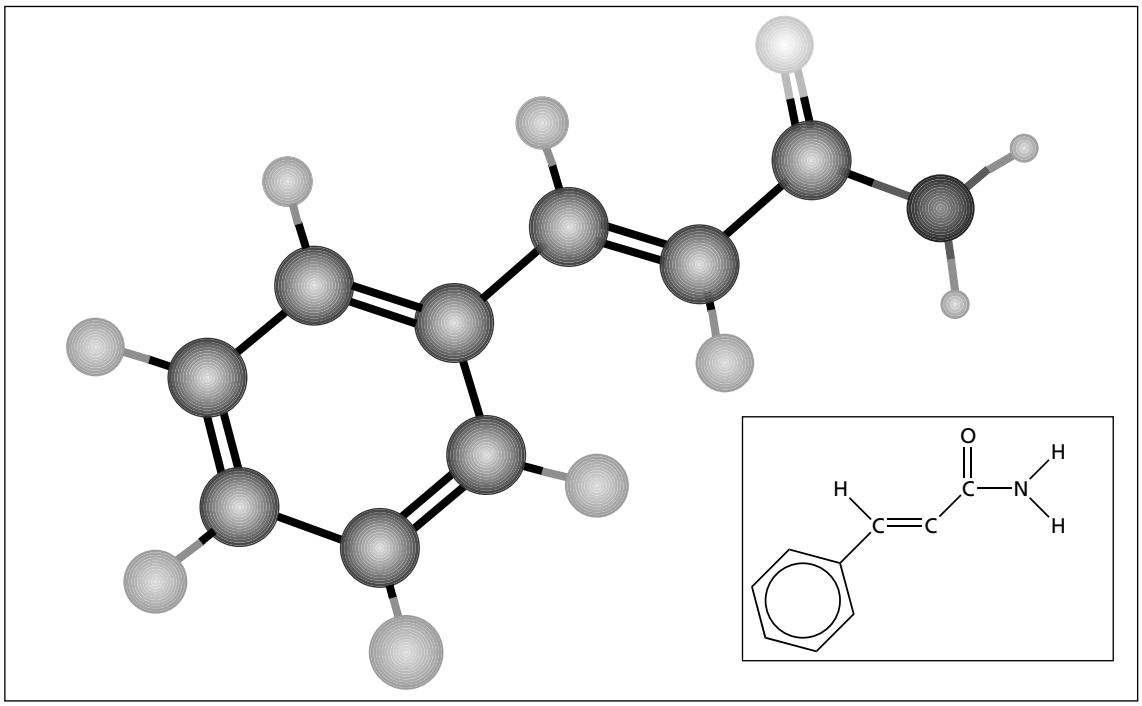


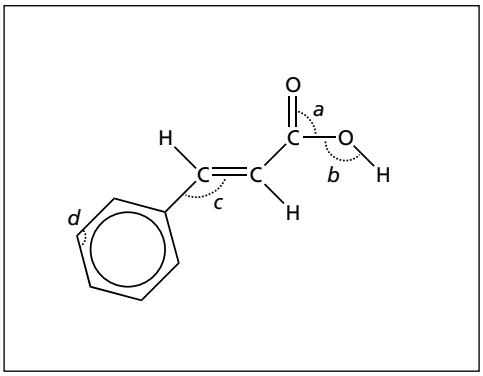
Figure 2
Main picture: the formula of cinnamamide drawn using Chem-3D®

Inset Figure 2a: The displayed formula of cinnamamide

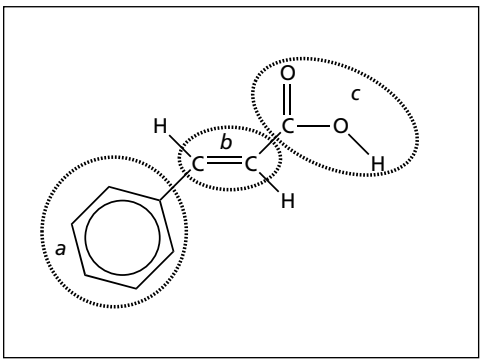
Cinnamamide is relatively soluble in water and reacts with water. This means that it is not very persistent after being applied, and work is being done to investigate ways of making it stick better to seeds.

•Questions

1. **Suggest how cinnamamide could be made from cinnamic acid.**
2. **Suggest at least four other derivatives of cinnamic acid which could be made from it in one step. Give the reactants and conditions.**
3. **Explain why cinnamamide might be expected to be slightly soluble in water.**
4. **Give a balanced equation for the reaction of cinnamamide with water. What type of reaction is this?**
5. **What values would you predict for the bond angles marked on the displayed formula of cinnamic acid below?**



6. **Cinnamic acid has three functional groups which are ringed on the displayed formula below. Name each one and say what type of reactions you would expect it to undergo. Give an example to illustrate each reaction type.**



7. **What is the systematic name for cinnamamide? Use the systematic name of cinnamic acid to help you.**
8. **Give the structure of the geometrical isomer of cinnamamide.**
9. **Make a model of cinnamamide using a ball and stick modelling kit. Which bonds can rotate and which cannot?**

•Acknowledgement

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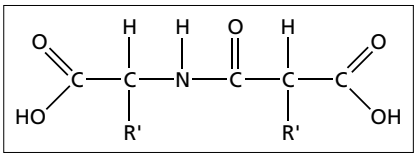
Answers...

•Combinatorial chemistry

1. ROH + R'COCl → R'COOR + HCl
2. Ethyl propanoate
3. HCl
4. 

5. The corresponding tripeptide, tetrapeptide *etc.*
6. Based on A-level chemistry, students might suggest the following:

a) Converting the $-CO_2H$ group into an ester

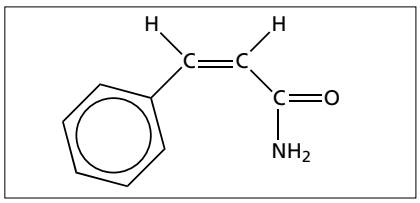
b) Converting the $-NH_2$ group into an N-substituted amine or an amide

However, neither of the compounds in (b) is really suitable as neither is easily removable.

7. Remove water as it is formed
8. Resin-A–C, resin–B–C and resin–C–C
9. 20^4 (160 000)
10. 3.6×10^9
11. a) High throughput screening for biological activity.
    b) Robotic techniques for synthesis. and sensitive analytical techniques

•Computational chemistry

1. React cinnamic acid with ammonia and then heat to dehydrate the ammonium salt produced.
2. Derivatives might include: ester, acid chloride, anhydride, salts and the parent alcohol, addition products of the double bond *etc.*
3. The $-CONH_2$ group can hydrogen bond with water but the rest of the molecule is non-polar so the solubility is not great.
4. $PhCHCHCONH_2 + H_2O \rightarrow PhCHCHCOOH + NH_3$

   A nucleophilic substitution reaction.
5. a ~120°, b ~105°, c ~121°, d = 120°
6. a) This is a benzene ring and undergoes electrophilic substitution reactions.
   b) This is an alkene and undergoes electrophilic addition reactions.
   c) This is a carboxylic acid and undergoes acid-base reactions and nucleophilic substitution reactions
7. *trans*-3-phenylprop-2-enamide.
8. 

9. The C-$CONH_2$ bond, the C–N bond and the C–Ph bonds can rotate, the others cannot.