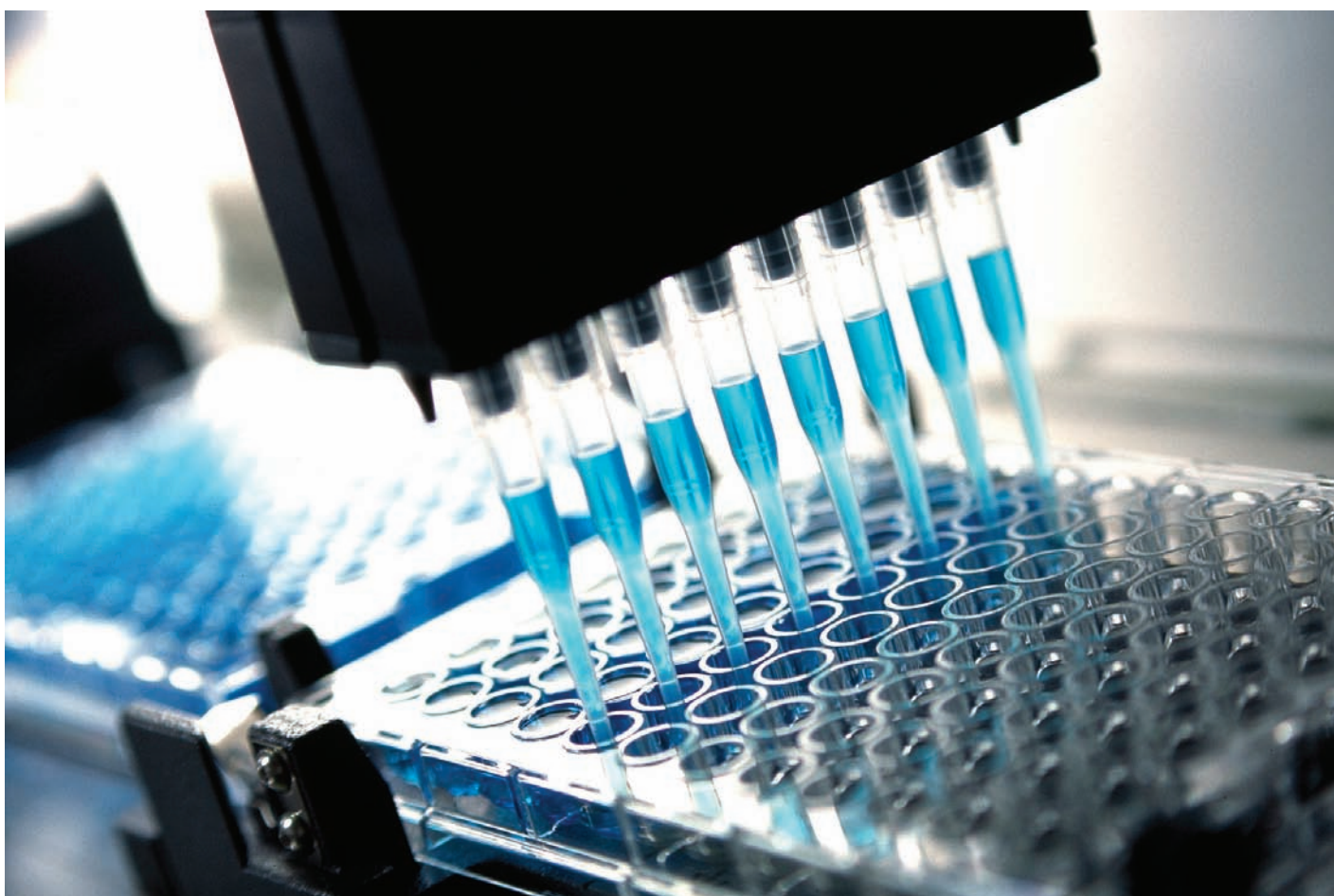


Synthesis and Analysis

Teacher Notes



Synthesis and Analysis is funded as part of the Reach and Teach educational programme supported by the Wolfson Foundation



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Synthesis and Analysis

Why focus on G&T and higher achievers?

Within the education system every child has the right to develop their learning so as to maximise their potential.

These exercises are designed to give students enthuse and enrich activities that although related to the curriculum are in fact taking the learning experience to the next level whilst also showing chemistry in a familiar context. This has been found to be a successful model for not only improving learning but also for raising levels of motivation. Higher achieving students can find the restraints of the standard curriculum to be demotivating leading to underachievement.

The different activities are designed to improve a number of skills including practical work/dexterity, thinking/analysis skills, literacy, research activities, use of models and teamwork. Students should also gain confidence through the activities and improve the ability to express themselves.

Some of the activities would appear to be complex for KS4, however at this stage in their learning high achieving students are open to new concepts and are ready to explore issues without pre-conceptions. They are keen to link ideas and develop concepts and understanding. It can prove to be an uplifting experience.

Introduction

Synthesis and analysis are two key aspects of chemistry, particularly when exploring the role of chemistry in an industrial context and relating the products formed to applications in everyday life.

In order to successfully synthesise any material it is necessary to have an understanding of the starting materials, the product(s) and the mechanisms and conditions needed to move from one to the other. This pulls together many different aspects of chemistry learning.

Once a product has been prepared it is important to be able to confirm that it is what was expected and also that it is pure. Analysis is a tool used to achieve this. In this range of activities the focus is upon chromatography, namely paper, thin layer and gas.

This programme is designed to develop students understanding of these topics from basic concepts to higher level thinking. It also aims to show that understanding how aspects of chemistry link together gives fuller understanding of the chemical processes as a whole. Working through the activities will also develop thinking and research skills.

Topic	Type of activity	Summary	Timing (mins)	KS3	KS4	KS5	Page
Synthesis Explorer	On-line tutorial	An excellent learning and tutoring tool for students who wish to explore synthesis, it is a curriculum-relevant resource.	Student centred			√	5
Design Studio	Interactive web assignment	An interactive web-based assignment to allow chemistry students to learn what is	Student centred			√	6

		involved in making a medicine.					
Chromatography of sweets	Practical	An introduction to paper chromatography and the analysis of mixtures.	30	√	√		15
The nitration of methyl benzoate	Practical	An activity that gives an insight into organic synthesis.	60		√	√	18
Aspirin	Practical	The synthesis of aspirin is followed by the analysis of the product and a calculation of yield.	75		√	√	21
Reaction mechanisms	Problem solving Misconceptions	This activity explores reaction mechanisms as the means of synthesis and explores misconceptions.	30+			√	26
Gas chromatography	Modelling practical	The use of a model to illustrate the separation techniques applicable to gas chromatography.	15		√	√	39

The first activity introduces synthesis in the form of an on-line tutorial whereby students can explore synthetic routes. They will gain knowledge of functional groups, mechanisms, and structure and shape. There is an opportunity to explore the structure and shape with 3D rotating models. This process is linked to the Design Studio where students work through an interactive activity looking specifically at molecules used in medicine.

The next activity introduces the basics of chromatography by undertaking paper chromatography of the colourants used in sweets. Not only does it show that different colours move different distances but also that the process can be used to separate the mixtures of colours used in certain sweets.

The next two activities are practical in nature and provide an opportunity to apply the principals of synthesis. The nitration of methyl benzoate applies the basic processes, whereas the manufacture of aspirin places the learning in a familiar context and also introduces analysis in the form of thin layer chromatography.

The investigation of reaction mechanisms and misconceptions ensures a clear understanding of the process of reactions and synthesis.

The final activity explores the use of a model to illustrate separation techniques as applied to gas chromatography. Such models are important in developing the understanding of students. They should be aware of the idea of models and also that they do have limitations.

Aims and objectives

The aims and objectives of these activities are:

- Developing questioning skills through problem solving.

- Exploring the use of models to expand understanding
- Develop practical skills and dexterity.
- Promote independent learning.

Chemistry topics:

- Functionality and molecular shapes
- Reaction mechanisms
- Synthesis routes
- Organic synthesis
- Theory and practice of chromatography
- Paper chromatography
- Thin layer chromatography
- Gas chromatography

These exercises can be used with key stages 3, 4, and 5 as indicated on the *Possible Routes*.

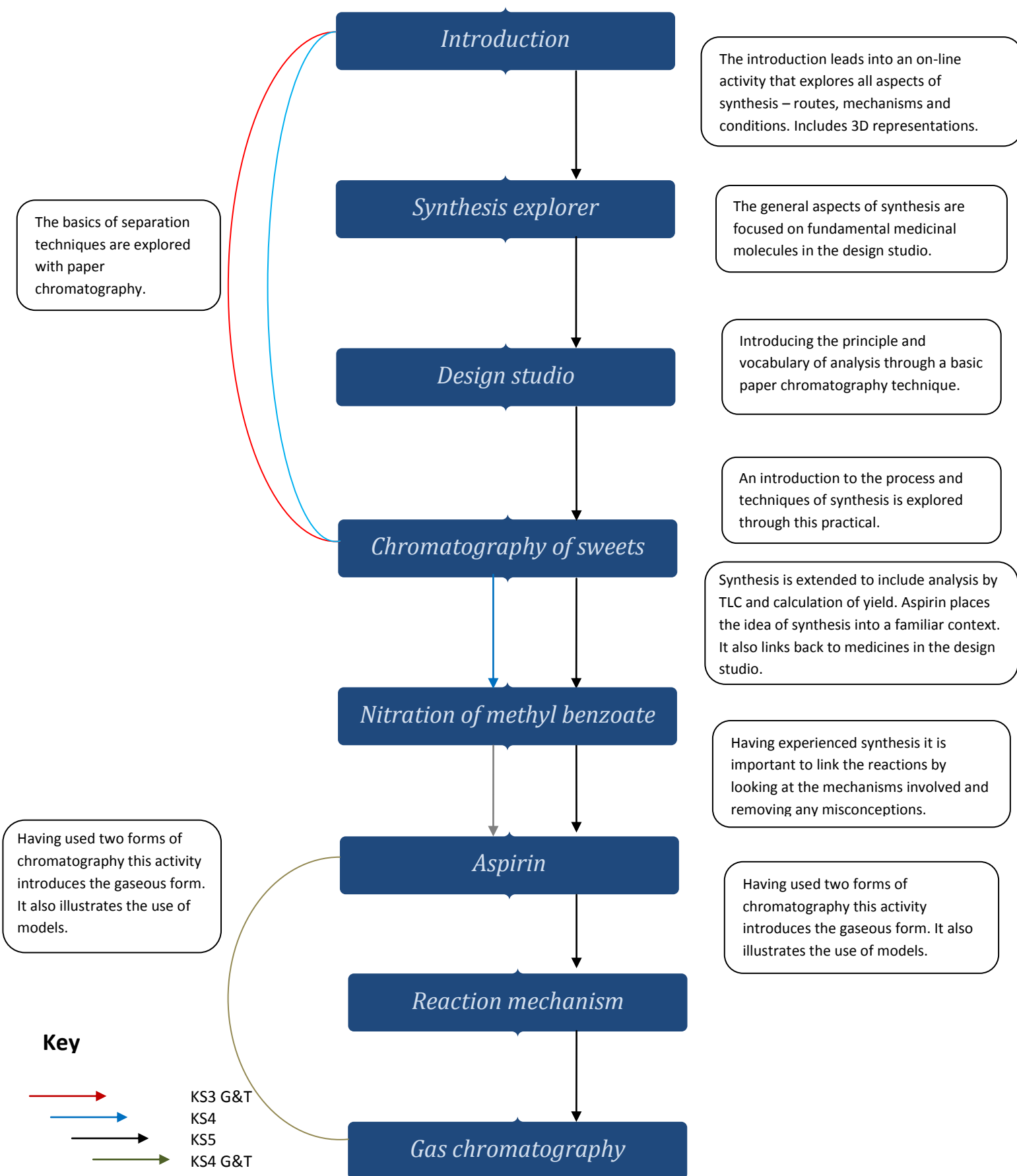
These activities have proved very successful with key stage 3 students who have followed the prescribed pathway and have been stimulated into further independent learning.

At key stage 4 a number of these activities are demanding but they do enhance understanding of key processes and show the application of higher order activities in a familiar context.

As well as developing key concepts and understanding, these exercises provide a reinforcement through an exploration of misconceptions and link together different pools of learning of the A level syllabus.

At all levels there is promotion of questioning skills, independent learning and research skills.

Possible routes

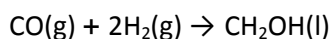


Synthesis

When two or more elements directly combine together to form a single new compound, this is usually called **synthesis** of the new compound. The term synthesis can also apply to much more complicated reactions involving a number of elements.

Organic synthesis

In Organic Chemistry (the chemistry of carbon), the term 'synthesis' often means something wider than joining atoms together. It is often used to mean the joining of small molecules together to make bigger molecules, or converting one type of molecule into another. The term still applies to the joining of materials to form a single new compound. The alcohol methanol, for example, can be made by the joining together of hydrogen and carbon monoxide under suitable conditions of heat and pressure with a catalyst being present. The equation for this reaction is:



In order to successfully synthesise a compound it is important not only to select the correct starting materials but also to have an understanding of which method and under what conditions, temperature, pressure etc, the reaction will produce the correct product. It is also worth remembering that many processes include more than one step, that is an intermediate substance(s) has to be synthesized in order to eventually produce the target material.

The opposite of synthesis is decomposition.

Activity 1: Synthesis explorer

<http://synthesisexplorer.rsc.org>

The link above opens a resource called Synthesis Explorer which as well as being a unique resource is an excellent learning and tutoring tool for students who wish to explore synthesis, it allows chemists to:

- choose a starting compound,
- react it, and then
- view details of the reaction
(conditions, reagents used and the classification).

Activity 2: Design studio

Design studio follows on from Synthesis Explorer in that allows students to explore the application of such molecules within the medical field therefore building a context within the learning episode.

<http://thedesignstudio.rsc.org>

Discover Chemistry has developed an interactive web-based assignment to allow chemistry students at post 16 level to learn what is involved in making a medicine. Students can learn about the shape, structure and interactions of molecules and what chemical properties are required to make effective medicines.

Aimed predominantly at post-16 students

- Introduction to diseases and the concepts of shape, enzyme inhibition, potency, drug-like properties and the balance of properties required for effective medicines.
- Students design and test molecules based on their knowledge of the enzyme active site and the properties of a range of substituents. They are able to view a 3D molecule model of their design bound in the enzyme active site before committing to a round of testing.
- A competitive advantage bar creates a sense of urgency and emphasises the importance of well-judged analysis, design and hypothesis-testing.
- At the end of the design round, students are tested in areas directly linked to the A-level curriculum - the more questions they get right, the more competitive their research becomes.
- When the student identifies one of the possible solutions, they can submit their candidate molecule for clinical development. At this stage, they are faced with the reality of the challenges and costs associated with the development of new medicines.

Analysis

Once a substance has been synthesized, analysis enables us to determine if the material produced is what was planned, are functional groups in the correct position/orientation. In this section we shall focus on the analysis of organic compounds.

The key area of analysis that will feature as an example is chromatography.

Chromatography

Chromatography is usually introduced as a technique for separating and/or identifying the components in a mixture. The basic principle is that components in a mixture have different tendencies to adsorb onto a surface or dissolve in a solvent. It is a powerful method in industry, where it is used on a large scale to separate and purify the intermediates and products in various syntheses.

The theory

There are several different types of chromatography currently in use – ie paper chromatography; thin layer chromatography (TLC); gas chromatography (GC); liquid chromatography (LC); high performance liquid

chromatography (HPLC); ion exchange chromatography; and gel permeation or gel filtration chromatography.

Basic principles

All chromatographic methods require one static part (the stationary phase) and one moving part (the mobile phase). The techniques rely on one of the following phenomena: adsorption; partition; ion exchange; or molecular exclusion.

Adsorption

Adsorption chromatography was developed first. It has a solid stationary phase and a liquid or gaseous mobile phase. (Plant pigments were separated at the turn of the 20th century by using a calcium carbonate stationary phase and a liquid hydrocarbon mobile phase. The different solutes travelled different distances through the solid, carried along by the solvent.) Each solute has its own equilibrium between adsorption onto the surface of the solid and solubility in the solvent, the least soluble or best adsorbed ones travel more slowly. The result is a separation into bands containing different solutes. Liquid chromatography using a column containing silica gel or alumina is an example of adsorption chromatography (Fig. 1).

The solvent that is put into a column is called the eluent, and the liquid that flows out of the end of the column is called the eluate.

Partition

In partition chromatography the stationary phase is a non-volatile liquid which is held as a thin layer (or film) on the surface of an inert solid. The mixture to be separated is carried by a gas or a liquid as the mobile phase. The solutes distribute themselves between the moving and the stationary phases, with the more soluble component in the mobile phase reaching the end of the chromatography column first (Fig. 2). Paper chromatography is an example of partition chromatography.

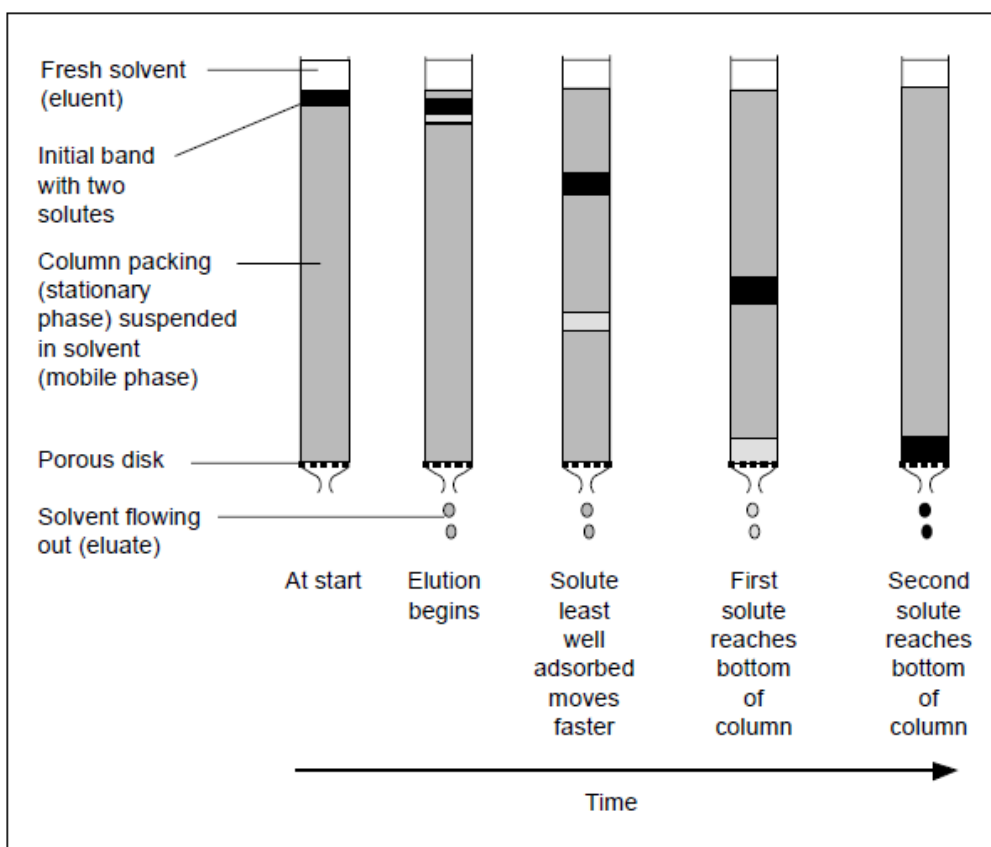


Figure 1 Adsorption chromatography using a column

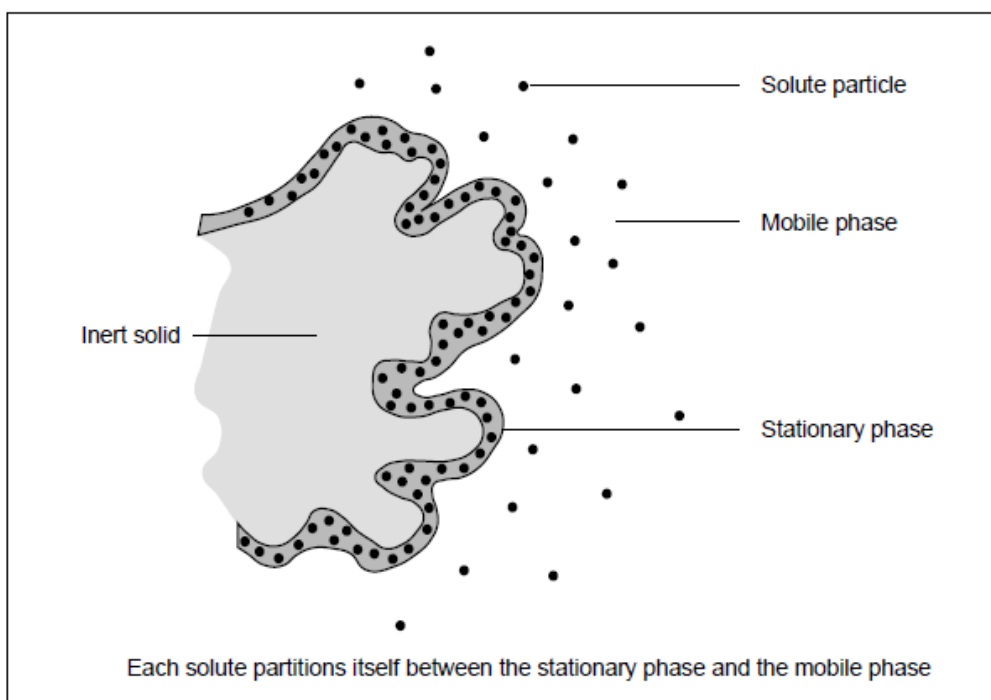


Figure 2 Partition chromatography

Paper chromatography

This is probably the first, and the simplest, type of chromatography that people meet.

A drop of a solution of a mixture of dyes or inks is placed on a piece of chromatography paper and allowed to dry. The mixture separates as the solvent front advances past the mixture. Filter paper and blotting paper are frequently substituted for chromatography paper if precision is not required. Separation is most efficient if the atmosphere is saturated in the solvent vapour (Fig. 3).

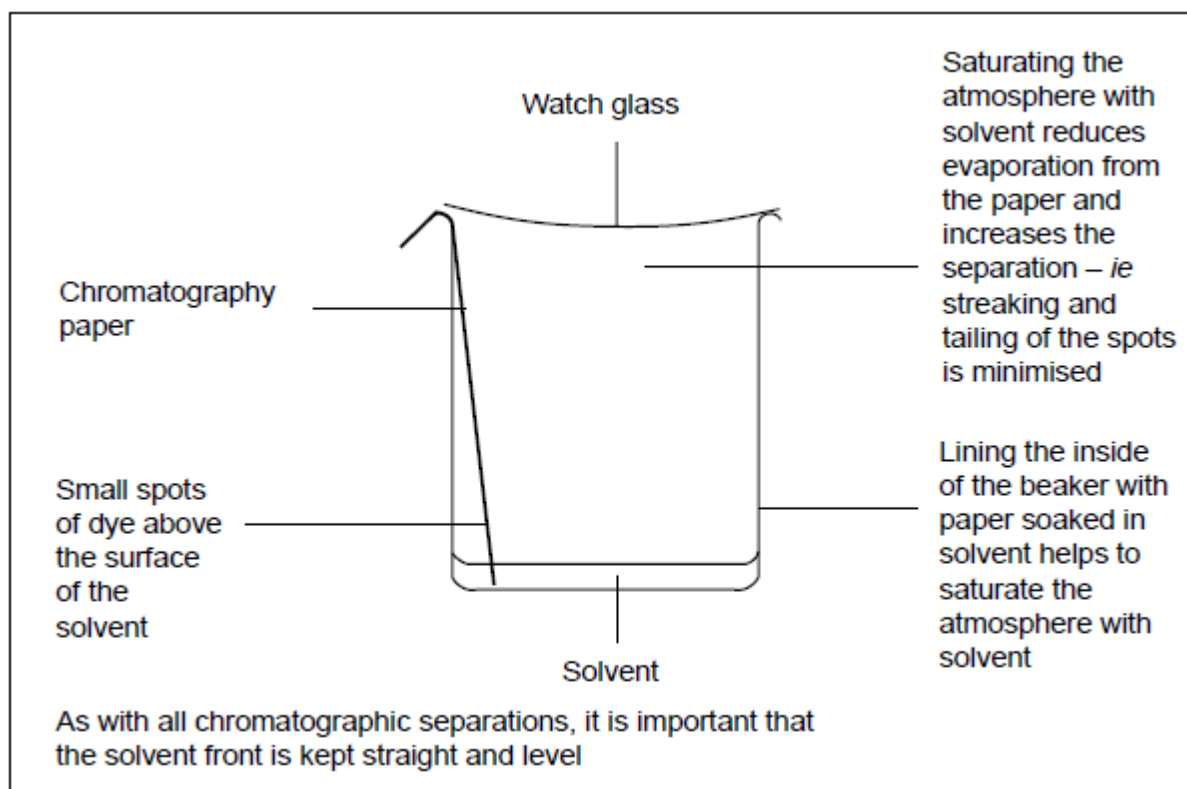


Figure 3 Paper chromatography

Some simple materials that can be separated by using this method are inks from fountain and fibre-tipped pens, food colourings and dyes. The components can be regenerated by dissolving them out of the cut up paper.

The efficiency of the separation can be optimised by trying different solvents, and this remains the way that the best solvents for industrial separations are discovered (some experience and knowledge of different solvent systems is advantageous). Paper chromatography works by the partition of solutes between water in the paper fibres (stationary phase) and the solvent (mobile phase). Common solvents that are used include pentane, propanone and ethanol. Mixtures of solvents are also used, including aqueous solutions, and solvent systems with a range of polarities can be made. A mixture useful for separating the dyes on Smarties is a 3:1:1 mixture (by volume) of butan-1-ol:ethanol:0.880 ammonia solution.

As each solute distributes itself (equilibrates) between the stationary and the mobile phase, the distance a solute moves is always the same fraction of the distance moved by the solvent. This fraction is variously called the retardation factor or the retention ratio, and is given the symbol R or R_f :

$$\text{Retention ratio} = \frac{\text{distance moved by solute}}{\text{distance moved by solvent}} = R_f$$

So as long as the correct solvent and type of chromatography paper are used, a component can be identified from its retention ratio (Fig. 4).

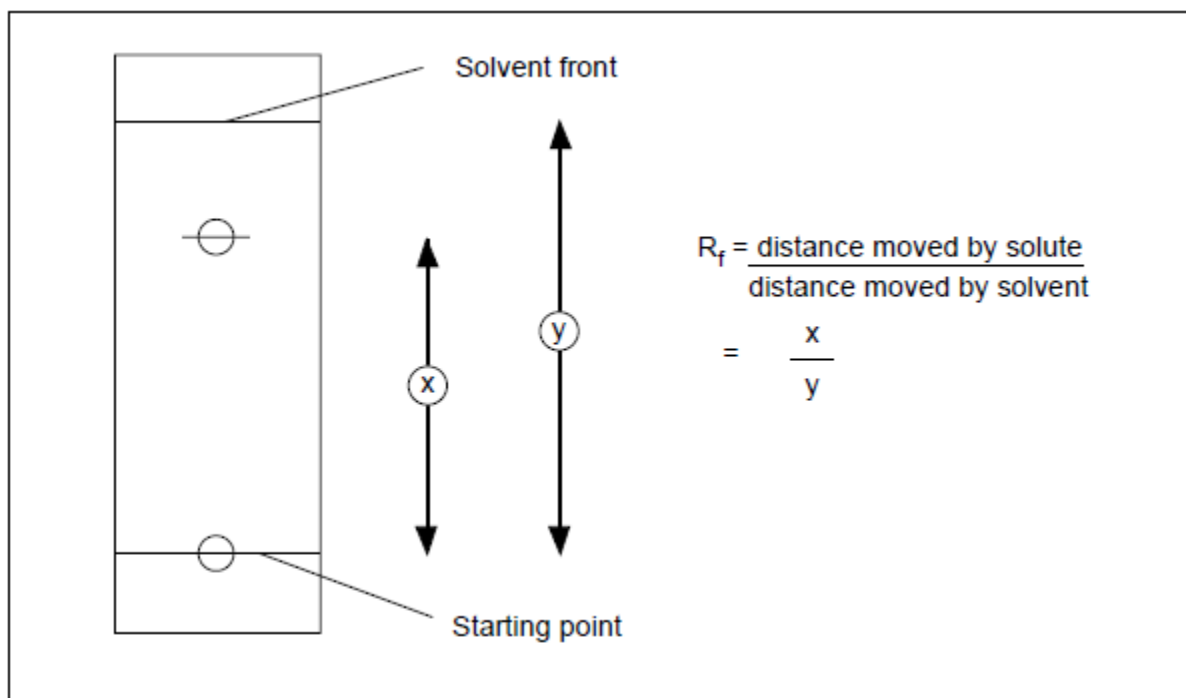


Figure 4 Retention ratio, R_f

It is possible that two solutes have the same R_f values using one solvent, but different values using another solvent (e.g. this occurs with some amino acids). This means that if a multi component system is not efficiently separated by one solvent, the chromatogram can be dried, turned through 90° , and run again using a second solvent as shown in figure 5.

Thin layer chromatography (TLC)

Thin layer chromatography is similar to paper chromatography, but the stationary phase is a thin layer of a solid such as alumina or silica supported on an inert base such as glass, aluminum foil or insoluble plastic. The mixture is 'spotted' at the bottom of the TLC plate and allowed to dry. The plate is placed in a closed vessel containing solvent (the mobile phase) so that the liquid level is below the spot. TLC has advantages over paper chromatography in that its results are more reproducible, and that separations are very efficient because of the much smaller particle size of the stationary phase.

The solvent ascends the plate by capillary action, the liquid filling the spaces between the solid particles. This technique is usually done in a closed vessel to ensure that the atmosphere is saturated with solvent vapour and that evaporation from the plate is minimised before the run is complete. The plate is removed when the solvent front approaches the top of the plate and the position of the solvent front recorded before it is dried (this allows the R_f value to be calculated).

TLC has applications in industry in determining the progress of a reaction by studying the components present; and in separating reaction intermediates. In the latter case a line of the reaction mixture is 'painted' across the TLC plate instead of a single spot, and the line of product after separation is cut out of the plate and dissolved in an appropriate solvent.

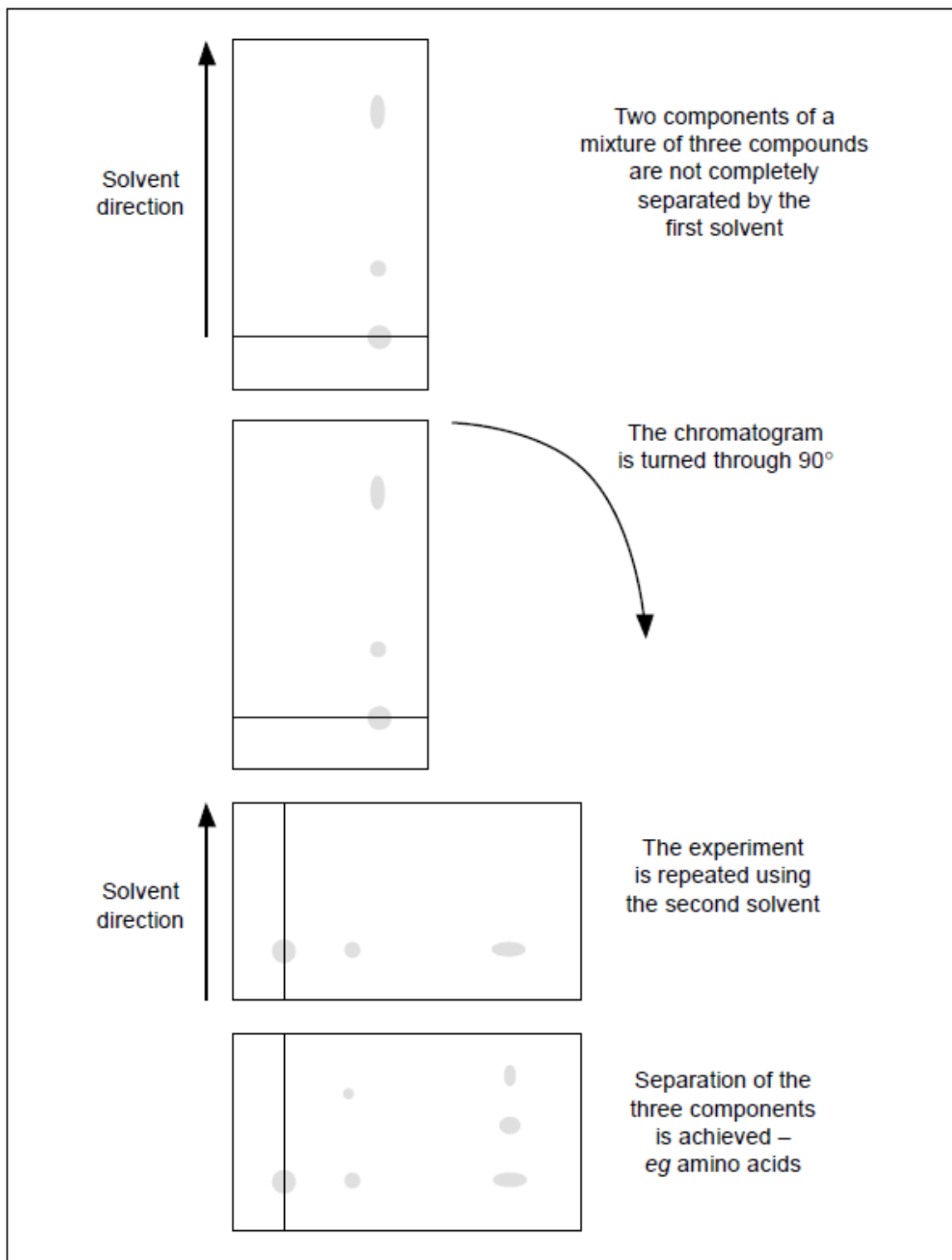


Figure 5 Using two solvents to separate a multicomponent mixture

Many spots are not visible without the plates being 'developed'. This usually involves spraying with a solution that is reversibly adsorbed or reacts in some way with the solutes. Two examples of developing solutions are iodine in petroleum ether (useful for identifying aromatic compounds, especially those with electron donating groups – eg $C_6H_5NH_2$) and ninhydrin (useful for identifying amino acids). Iodine vapour is also used to develop plates in some cases. Alternatively, specially prepared plates can be used that fluoresce in ultraviolet light. The plates are used in the normal manner, but once dried they are placed under an ultraviolet lamp. Solute spots mask fluorescence on the surface of the plate – ie a dark spot is observed. Some compounds have their own fluorescence which can be used for identification, or retardation factors can be used to identify known solutes.

The following model may help in the explanation of chromatography. The whole basis of chromatography is based upon the different affinity of substances within a mobile phase, liquid or gas, for a solid stationary phase.

Chromatography and Shopping

2 very different shoppers, Wayne and Amy

Wayne likes bookshops
and walking



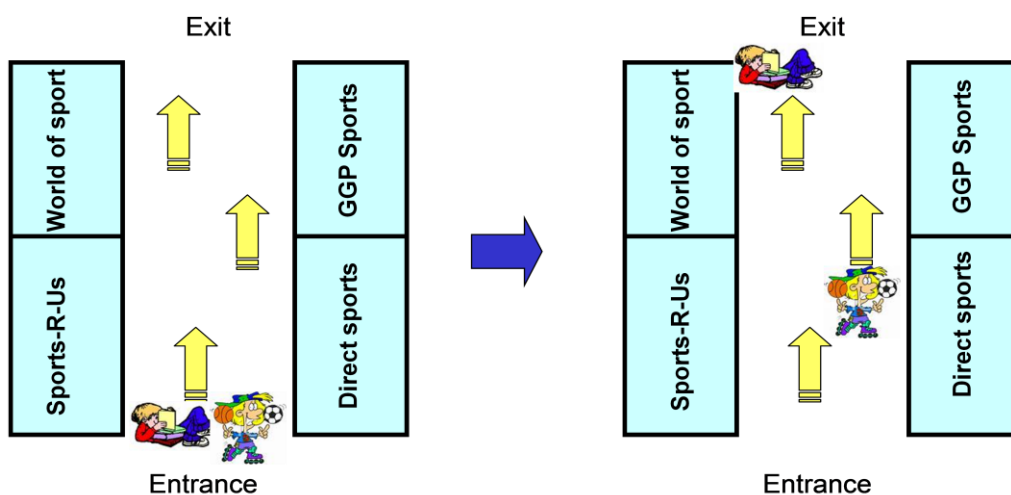
Amy likes sports shops
and roller-blading



Who is the quicker at shopping?

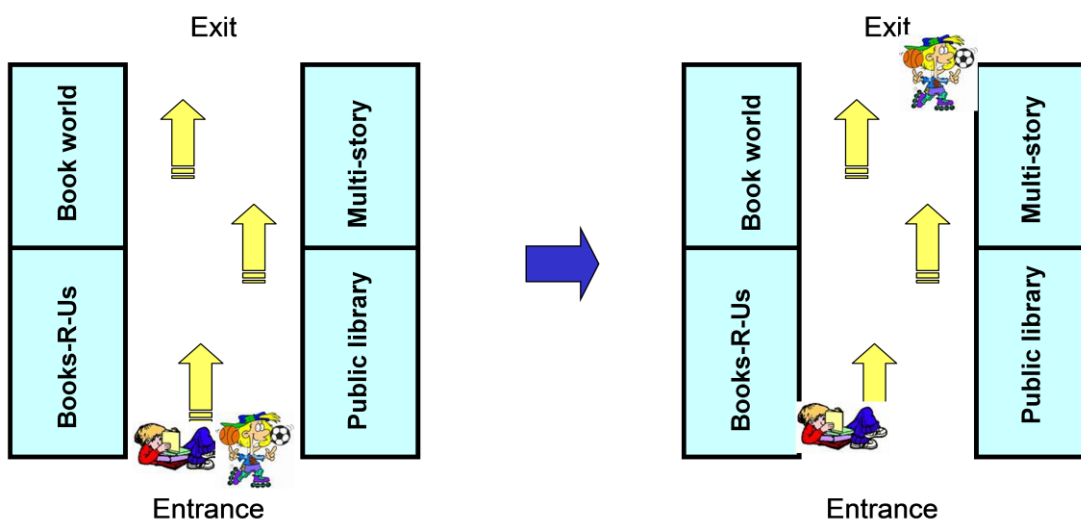
Wayne and Amy go shopping

- Shopping centre 1
 - Sports shops (no roller-blading)



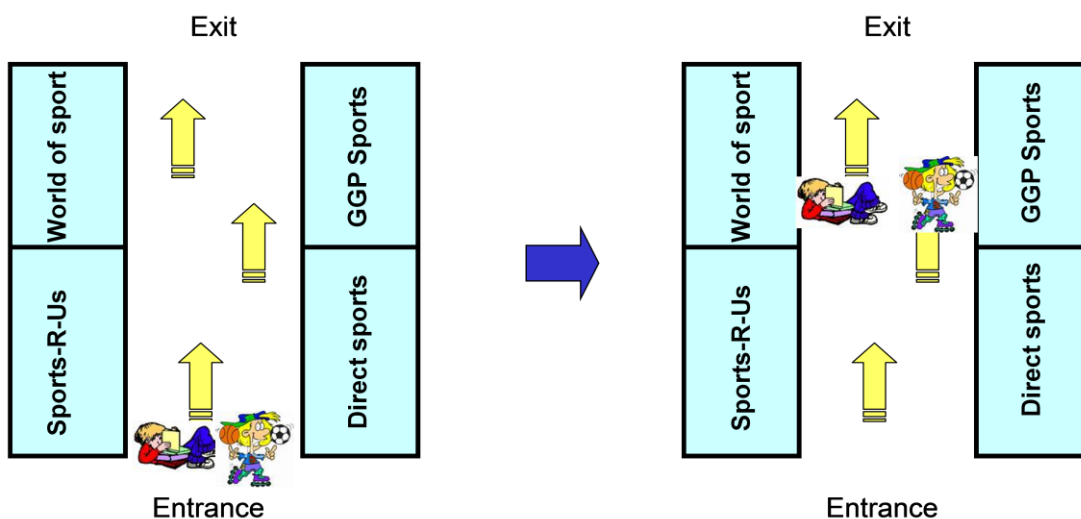
Wayne and Amy go shopping

- Shopping centre 2
 - Book shops (roller-blading allowed)



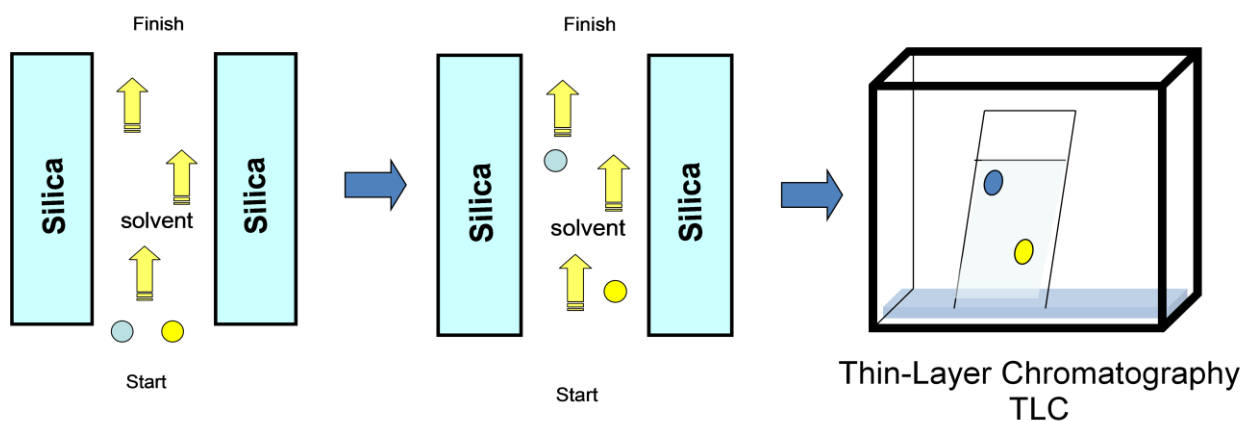
Wayne and Amy go shopping

- Shopping centre 3
 - Sports shops (roller-blading allowed)



So what's all this got to do with chromatography?

compound 1 ● and compound 2 ●



A simple experiment illustrating this principle uses coloured sweets and paper as a stationary phase.

Activity 3: Chromatography of sweets

Teacher notes

This type of experiment goes down well with students since it uses well known material normally used as confectionery. The coloured dye coating the surface is removed from M&M'S® of various colours. A spot of each is put on to a piece of chromatography paper and water is allowed to soak up the paper separating out the component dyes. The results show which dye mixtures are used to produce particular colours for the sweets.

Lesson organisation

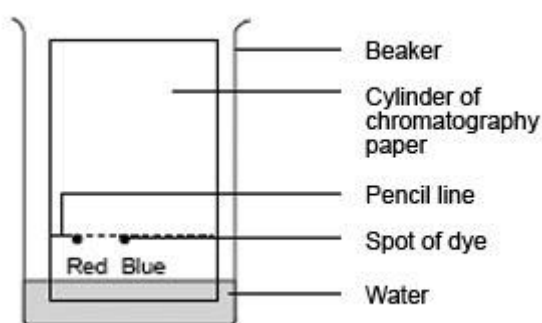
Students should have a good basic understanding of chromatography theory and this practical can be a useful introduction to the method of separation. The experiment can be carried out by groups of two or three and takes about 30-40 minutes. Students must be told that the M&M'S® are not to be eaten under any circumstances.

Procedure

HEALTH & SAFETY: Students must not attempt to eat the M&M'S® or even lick them. They are for laboratory use only.

- Place the piece of chromatography paper on a clean flat surface, with the longer side horizontal and draw a horizontal line in pencil (not biro) about 1.5 cm from the base of the paper.

- b) Use the dampened paint brush to remove the colour from one of the M&M'S® and paint this colour on the line about 2 cm from one end. Small spots are best.
- c) Clean the brush in fresh running water and paint the colour of another M&M® on the line about 2 cm from the first spot.
- d) Repeat this until all the colours are on the paper or until you have reached the other end.
- e) Use a pencil (not a biro) to write the name of the colour next to the corresponding spot.
- f) Roll the paper into a cylinder and hold this in place with the paper clips. Try to avoid any overlapping of the paper when you make the cylinder.
- g) Put water into the beaker up to depth of about 1 cm.
- h) Lower the paper cylinder into the beaker of water thus allowing the water to rise up the paper. Ensure that the water is below the level of the spots. Try to avoid moving the paper cylinder about once it is in position.
- i) When the water approaches the top of the paper cylinder remove it from the water. Mark with a pencil the level of the water at the top of the filter paper.



- j) Allow the paper cylinder to dry, perhaps by using a hairdryer if available or by clamping it and leaving it to dry overnight.
- k) Unravel the paper cylinder and examine it carefully.

Teaching notes

Encourage the students to make small intense spots on the paper and to avoid smudging.

Some dyes will be found to produce only one spot further up the paper, whilst others will have spread into two or more areas of colour.

If appropriate students should be told that the relative distance travelled by each “spot” depends not only on its solubility in water but also on its attraction for the cellulose components of the paper.

It should be emphasised that each “spot” may well still be a mixture of dyes, and that a more effective separation might occur:

- if the distance travelled by the spots is increased, e.g. by using a taller cylinder in a taller beaker.
- with a different solvent, other than water
- with a different stationary phase (e.g. silica plates).

Student questions

Here are some questions for students.

- a) Why do you think some dyes separate out into different colours whilst others do not ?

- b) Why do you think some colours move further up the paper than others ?
- c) Can you think of any way of improving the separation between the different spots ?
- d) Look on the side of a M&M'S® packet for a list of the coloured dyes used. Try to identify which dyes correspond to the spots on the chromatogram.

Chromatography of sweets

Technician notes

Apparatus and chemicals

Beaker (250 cm³)

Small soft paint brush

Paper clips (preferably plastic coated), 2

Chromatography paper, approximately 20 cm x 10 cm (see note 1)

Pencil

Ruler

A communal hairdryer (optional) (see note 2)

A supply of M&M'S® of various colours (see notes 3 and 4)

Technical notes

1. Whatman chromatography paper works best for this experiment, but, if unavailable, large sheets of ordinary filter paper can be cut up instead.
2. Ensure that the hairdryer has had an electrical safety check.
3. M&M'S® with a variety of about 6 or 7 different colours are required for each group.
4. If M&M'S® are unavailable this experiment can be carried out with liquid food colouring which is readily available from supermarkets. Chromatography of Smarties® is less successful as they use natural food colourings. Peanut M&M'S® should not be used if there are students with peanut allergies.

As a means of investigating the basic principles of synthesis, the following experiment that follows the nitration of methyl benzoate is a good example. Not only does it bring into practice a number of standard techniques it also looks closely at the mechanisms involved.

The aspirin synthesis not only puts the idea of synthesis into a familiar context but it develops into analysis by thin layer chromatography and the calculation of yield. There is also a link to the ideas developed in the Design Studio activity.

Activity 4: The Nitration of Methyl Benzoate

Apparatus and chemicals

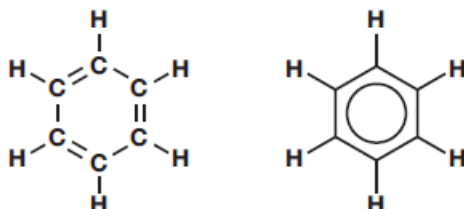
- concentrated sulfuric acid (**corrosive**) See CLEAPSS Hazcard 98A and Recipe Book sheet 98
- concentrated nitric acid (**corrosive**) See CLEAPSS Hazcard 67 and Recipe Book sheet 61
- methyl benzoate (**harmful**) See CLEAPSS Hazcard 64
- deionised water
- crushed ice
- ice baths
- thermometers
- dropping pipettes (eg 'calibrated' plastic)
- Buchner flasks
- Buchner funnels and suitable sized filter paper
- ethanol (**Highly Flammable**) See CLEAPSS Hazcard 40A
- steam baths
- melting point apparatus
- conical flasks
- beakers
- stirring rods
- water bottles
- large filter papers

HEALTH & SAFETY

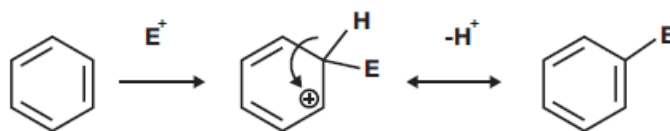
Laboratory coats, disposable nitrile gloves and safety goggles must be worn at all times. Conc. Sulfuric acid and conc. Nitric acid must be measured in a fume cupboard. No naked flames should be present while ethanol is being used.

This activity is designed to give you an insight into what organic chemists do in their day to day work.

A wide range of organic molecules, both naturally occurring and man-made, such as therapeutic medicines and dyes are aromatic compounds. The simplest aromatic compound is benzene.



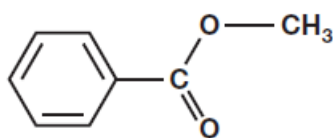
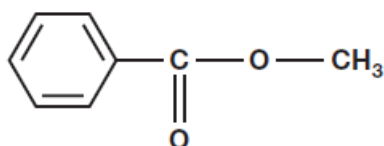
Aromatic compounds normally undergo substitution reactions – rather than addition reactions. This is because substitution reactions retain the delocalised π -electron system of the aromatic nucleus.



One of the most important substitution reactions of aromatic compounds is nitration – *ie* the addition of an NO_2 group.

The experiment

In this experiment you will nitrate methyl benzoate, which is a relatively simple non-toxic derivative of benzene. You will use a mixture of nitric acid and sulfuric acid to carry out the nitration and then purify the product by recrystallisation.



Finally you will determine the structure of the nitro compound that you have made. How many nitro groups you have added to the ring, and where? You will use a range of spectroscopic techniques – mass spectrometry (MS), infrared (IR) spectroscopy and nuclear magnetic resonance (NMR) spectroscopy – to work out the answer.

The procedure

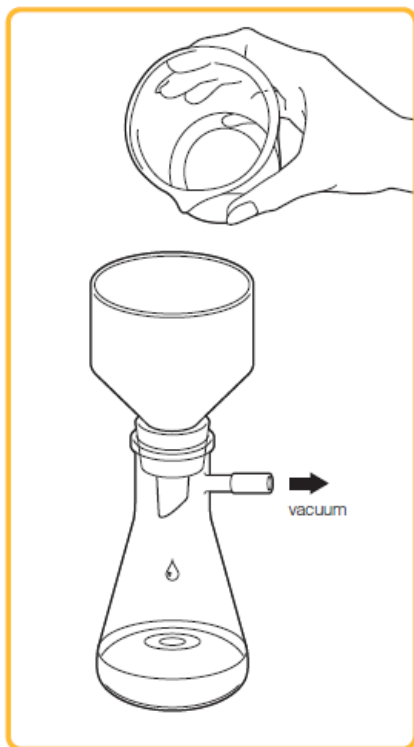
- 1 Measure 2.5 cm³ of methyl benzoate into a small conical flask and then dissolve it in 5 cm³ of concentrated sulfuric acid. When the liquid has dissolved, cool the mixture in ice.
- 2 Prepare the nitrating mixture by carefully adding 2 cm³ of concentrated

sulfuric acid to 2 cm³ of concentrated nitric acid. Cool this mixture in ice.

3 Add the nitrating mixture – drop by drop from a teat pipette – to the solution of methyl benzoate. (NB: Do not allow the nitrating mixture to get into the rubber teat.) Stir the mixture with a glass rod and keep the temperature below 10 °C. When you have completed the addition, leave the mixture to stand at room temperature for another 15 minutes.

4 After 15 minutes, pour the reaction mixture on to about 25 g of crushed ice and stir until all the ice has melted and the crystalline nitro derivative forms.

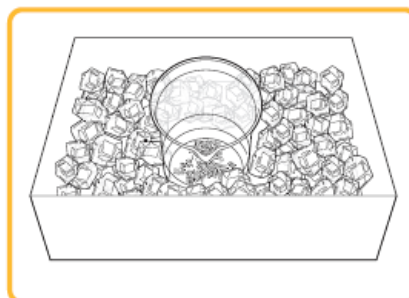
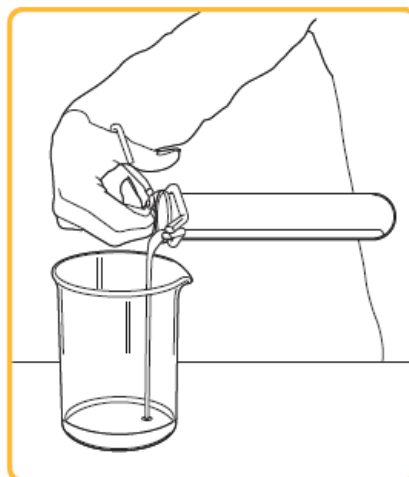
5 Filter the crystals using a Buchner funnel, wash thoroughly with cold water and then transfer to a small beaker.



6 Recrystallise the product from hot ethanol. The idea of recrystallisation is to dissolve the impure product in the minimum possible volume of hot solvent. When you cool the solution, the product that you want crystallises out of solution. This is because there is not enough solvent to dissolve it all at the lower temperature. However, the impurities stay behind in solution, because there are less of these

impurities there is enough solvent to keep them dissolved. You then filter off the crystals of the product from the remaining solution.

7 Put 15 cm³ of ethanol in a boiling tube. Warm it to about 50 °C on the steam bath. Dissolve all the crystals in possible volume of this hot solution to cool to room temperature then immerse the beaker in ice to complete the crystallisation.



8 Filter the crystals and dry them between filter paper. If there is time, measure the melting point of the crystals.

Activity 5: Aspirin

A RISK ASSESSMENT MUST BE DONE FOR THIS ACTIVITY

Materials required

- 250 cm³ round bottom flask
- reflux condenser
- Buchner flask
- Buchner funnel
- water bath
- watch glass
- 250 cm³ conical flask
- ethanoic anhydride (**corrosive**) See CLEAPSS Hazcard 39
- concentrated sulfuric acid (**corrosive**) See CLEAPSS Hazcard 98A
- 2-hydroxybenzoic acid (**harmful**) See CLEAPSS Hazcard 52
- ethanol (**highly flammable**) See CLEAPSS Hazcard 40A
- TLC solvent – acetonitrile/ethanoic acid/water
 - acetonitrile (**highly flammable & harmful**) -There is no CLEAPSS Hazcard for acetonitrile. This chemical is not normally available/used in schools and so a special Risk Assessment is required.
 - ethanoic acid (**harmful & corrosive**)
- TLC solvent tanks

HEALTH & SAFETY

Wear goggles (not safety spectacles). Handle ethanoic anhydride in a fume cupboard.

The produced 2-ethanoyloxybenzenecarboxylic acid (aspirin) is **harmful**. See CLEAPSS Hazcard 52.

aspirin

the wonder medicine

Nearly all of us have used aspirin at some time in our lives, but not many people know that for hundreds of years a related compound from willow bark was used to relieve pain and treat fevers. Ancient Asian records show it was used 2400 years ago.

In the 1890s Felix Hoffman of the Bayer Company in Germany made aspirin, which was found to have good medicinal properties. In 1898 aspirin was sent for clinical trials and Bayer patented the process. In 1915 during World War One the British very much wanted aspirin and the British government offered a substantial reward to anyone who could develop a manufacturing process. A Melbourne

pharmacist, George Nicholas, did just that.

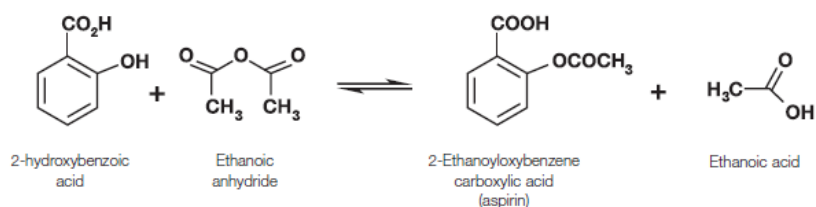
Approximately 35,000 metric tonnes are produced and consumed annually, enough to make over 100 billion standard aspirin tablets every year. Nowadays aspirin is not only used as a pain killer but has also been proposed as effective in reducing the incidence of heart disease.

This practical session aims:

- to introduce you to the synthesis of one of the oldest medicines, aspirin
- to analyse the purity of your aspirin using techniques you will not have used in school.

Synthesising aspirin

Aspirin is a relatively simple molecule containing an ethylated phenol group and a carboxylic acid group. In your experiment you will make aspirin from an acid called 2-hydroxybenzoic acid by esterification with ethanoic anhydride under acid catalysed conditions. Ethanoic anhydride is an 'activated' form of ethanoic acid which most of you will have encountered in its dilute form as the vinegar you put on fish and chips. Using ethanoic anhydride ensures that the esterification reaction goes to completion much more quickly than if you use ethanoic acid. Why is ethanoic anhydride more effective than ethanoic acid? Also, why is H^+ added? Once you've made the aspirin you'll then need to purify it by recrystallisation from a suitable solvent.



Materials that are made for human consumption must be checked thoroughly to ensure that:

- the material is the correct product; and
- it is highly pure.

Checking the purity of a sample can be done in a variety of ways and you will be using traditional 'wet' chemistry techniques as well as more advanced spectroscopic techniques to determine the purity of your sample.

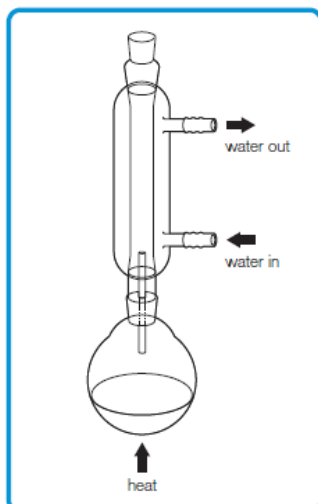
The experiment

1 Collect a 250 cm³ round bottom flask containing ethanoic anhydride (8.0g) and concentrated sulfuric acid (3 drops).

2 Collect 5 g of 2-hydroxybenzoic acid. Add the 2-hydroxybenzoic acid in small portions to the ethanoic anhydride/concentrated



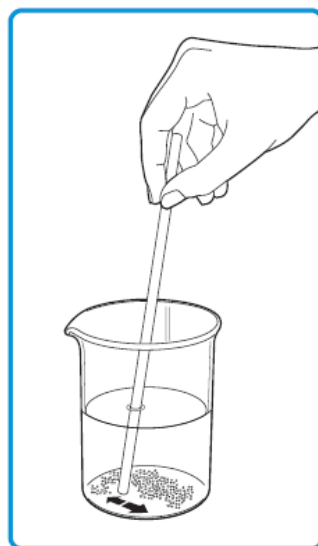
sulfuric acid mixture. Gently swirl the flask after each addition of 2-hydroxybenzoic acid so that it is mixed with, and dissolves in, the ethanoic anhydride. When all the 2-hydroxybenzoic acid is added there may be some solid which will not dissolve – do not worry as this is normal.



3 Connect a reflux condenser to the round bottom flask and heat the reaction mixture under reflux in a water bath for 15 minutes.

4 Then add water (60 cm³) and swirl the reaction mixture to ensure complete mixing.

5 Leave the reaction mixture to cool for about 10 minutes. The crude aspirin should crystallise from solution at this stage. If you do not have a solid, do not panic this can happen to even the most experienced organic chemists! The problem can be overcome by 'scratching' the reaction flask with a glass rod – one of the demonstrators will show you how to do this.



6 Filter off the white, crude aspirin solid under vacuum using a Buchner flask and funnel, wash the product with ice cold water (20 cm³) and then leave the solid to suck as dry as possible.

7 Save a small portion of the crude aspirin (about 0.1 g).

8 Recrystallise the rest of the product as follows.

9 Carefully transfer your crude aspirin into a round bottom flask then connect the condenser. Gradually, add ethanol and heat the mixture under reflux using a water bath until the solid dissolves. This should require approximately 15-20 cm³ of ethanol.

10 Transfer the solution to a 250 cm³ beaker and leave the clear, colourless solution to cool to room temperature slowly, during which time crystallisation of aspirin should begin.

11 Collect the recrystallised aspirin, which should be white, using the Buchner flask and funnel.

12 Use the filtrate to transfer any remaining crystals from the beaker to the funnel.

13 When all of the solid has been carefully collected in the Buchner funnel, wash the crystals with ice cold ethanol (10 cm³) and allow the solid to suck as dry as possible for about five minutes.

14 Transfer the crystals to a watch glass and allow to air dry for at least 15 minutes.

15 Weigh the dry, purified aspirin product.

16 Measure the melting range of your dried product.



SAFETY

The reaction should be done in a fume cupboard.

The results

Weight of recrystallised product	= _____ g
Melting point range	= _____ - _____ °C
Literature m.p.	= _____ 138-140 °C

Theory and percentage yield of product

An organic chemist always calculates the % yield of the product obtained using the following procedure.

- 1 The number of moles of each reagent used in the reaction is worked out.
- 2 The limiting reagent, the reagent that is present in the lowest number of moles, is identified.
- 3 We then assume that if every single molecule of this reagent was converted to the product this is the maximum amount of product that could be obtained. This is known as the 100% or theoretical yield.
- 4 The actual % yield is calculated.

The following steps are followed to obtain the required information:

Molecular formula of ethanoic anhydride	= C ₄ H ₆ O ₃
Molecular weight of ethanoic anhydride	= (4 x) + (6 x) + (3 x)
Number of moles of ethanoic anhydride	= weight of ethanoic anhydride used ÷ molecular weight of ethanoic anhydride
Number of moles of ethanoic anhydride	= _____ mol
Molecular formula of 2-hydroxybenzoic acid	= _____
Molecular weight of 2-hydroxybenzoic acid	= _____
Number of moles of 2-hydroxybenzoic acid	= _____
The limiting reagent	= _____
Molecular formula of aspirin	= _____
Molecular weight of aspirin	= _____
Theoretical yield	= no. of moles of limiting reagent * Molecular weight of the product
∴ Theoretical yield	= _____ g
% yield	= (actual yield/theory yield) x 100
	= _____ (/) * 100
% yield	= _____

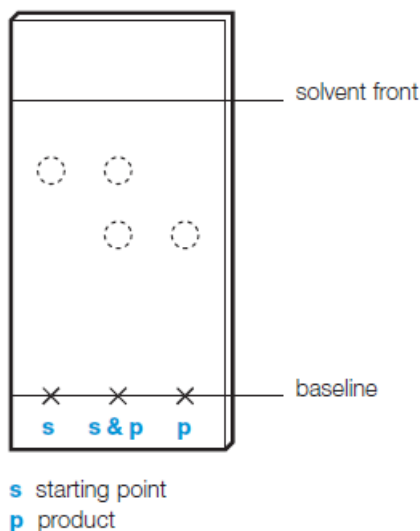
Purifying and identifying aspirin

Thin layer chromatography (tlc)

You've probably used simple chromatography as part of your earlier studies to separate the dyes in coloured ink. In this activity you investigate the purity and identity of your laboratory prepared aspirin samples using thin layer chromatography (tlc).

Thin layer chromatography is a rapid separation technique, which means that a pure substance gives 'one spot'. However, if extra spots are observed as well as the characteristic pattern of the known compound, then impurities are likely to be present in the sample. (What impurities are likely to be present in your sample?) You can also identify 'unknown' compounds by comparing their R_f values (the distance travelled by the component spot/distance travelled by the solvent front) with an authentic standard running on the same plate.

You'll see a demonstration of how to run a tlc of your product. The solvent system used to run your tlc is a mixture of acetonitrile/ethanoic acid/water (why do the different components travel different distances on the TLC plate?).



Tlc results for crude and recrystallised aspirin

TLC results for crude and recrystallised aspirin

Sample	Crude Aspirin	Recrystallised Aspirin
Number of spots observed		
Distance travelled by solvent front (mm)		
Distance travelled by UV active spots (mm)	1 2 3	
R_f Values	1 2 3	

You will also run an infrared (IR) spectrum of the product and compare it with the spectrum of pure aspirin. If they are identical your synthesis of aspirin has been successful. You will also see demonstrations of both a nuclear magnetic resonance (NMR) spectrometer and high performance liquid chromatography (HPLC).

3

Having explored some of the aspects of synthesis it is important to ensure that the knowledge and understanding of mechanism is sound. The following activity explores this knowledge and understanding, and also searches out any possible misconceptions.

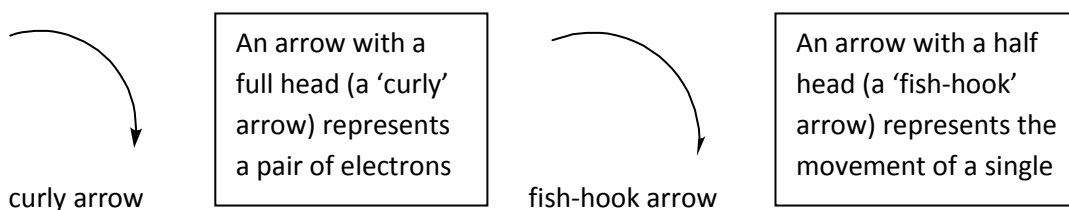
Activity 6: Reaction mechanisms

Chemists use reaction mechanisms to show what they think might be happening as molecules interact during chemical reactions.

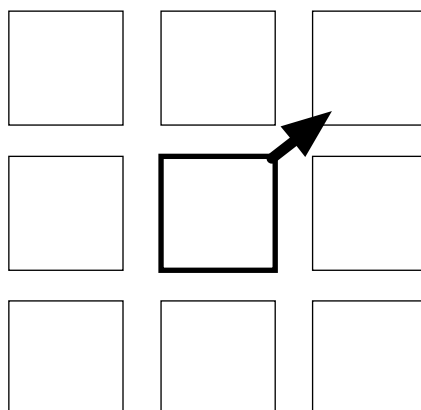
When drawing reaction mechanisms the chemist usually assumes:

1. that the reaction occurs in several distinct steps;
2. that each step can be represented as the movement of electrons; and
3. that sometimes electrons move as pairs, and sometimes they move individually.

Diagrams showing the steps in reaction mechanisms usually show the molecules and/or ions (shown by + and -) and/or radicals (shown by •) involved, as well as arrows showing the movement of electrons. Two types of arrows are used:

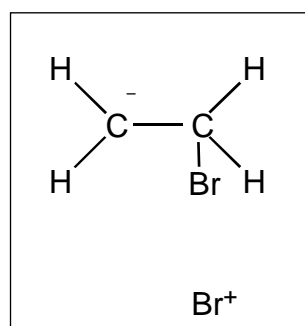
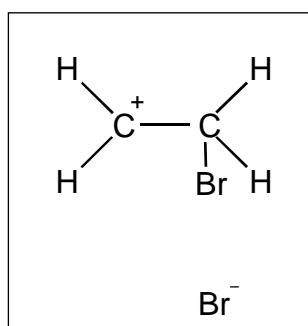
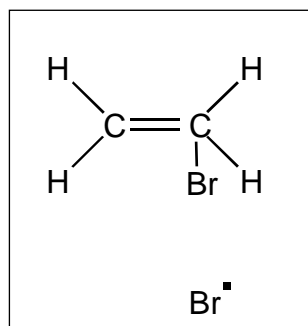
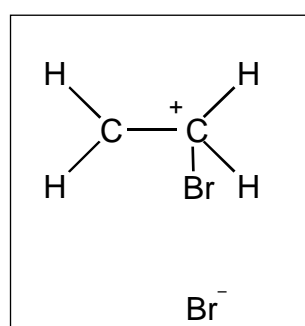
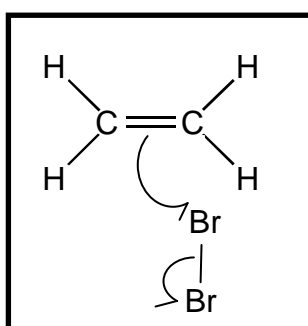
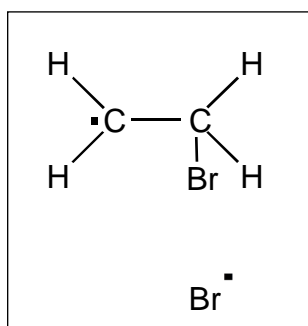
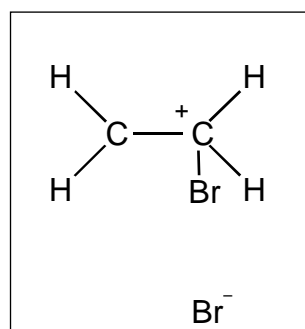
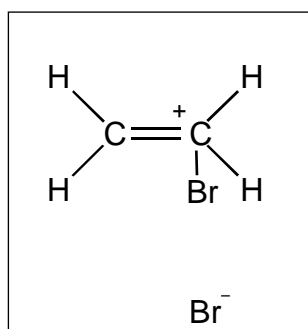
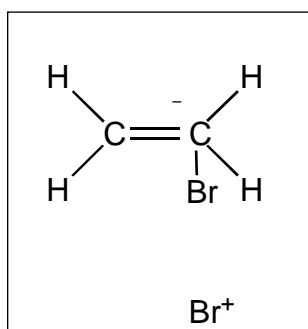


There are two questions in this exercise. The questions each consist of a central diagram showing the initial stage in a reaction mechanism, surrounded by a selection of suggestions for the result of that step. Your task in each case is to identify which of the diagrams gives the correct outcome of that reaction step. Draw a large arrow showing which diagram is correct, as in the example below.



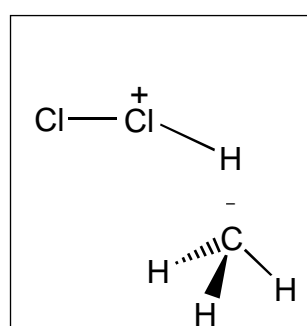
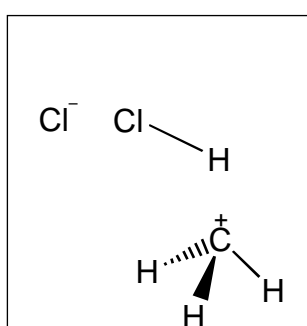
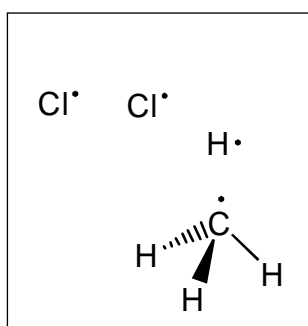
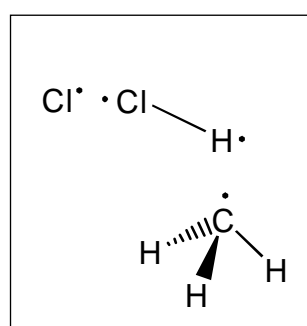
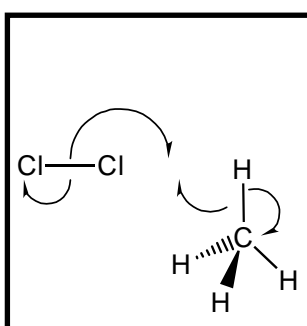
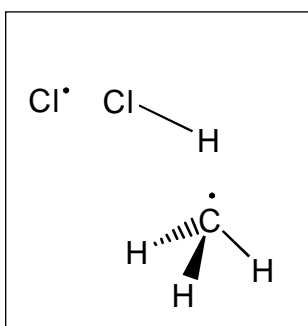
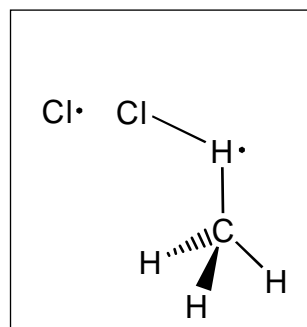
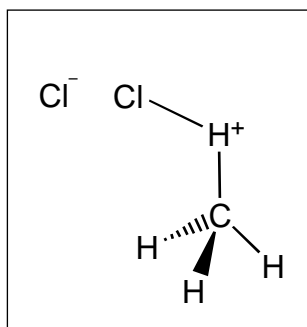
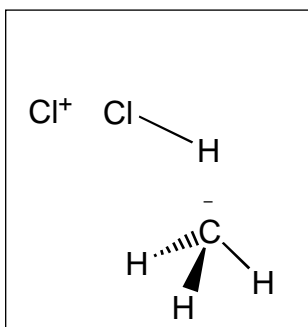
Try and explain your reason(s) for selecting the diagram you chose.

Reaction mechanism 1



I selected this diagram because:

Reaction mechanism 2

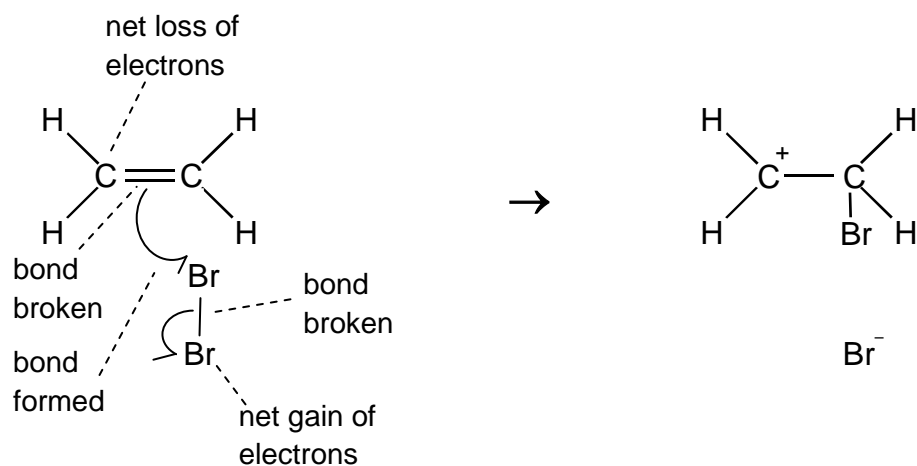


I selected this diagram because:

Reaction mechanisms revealed

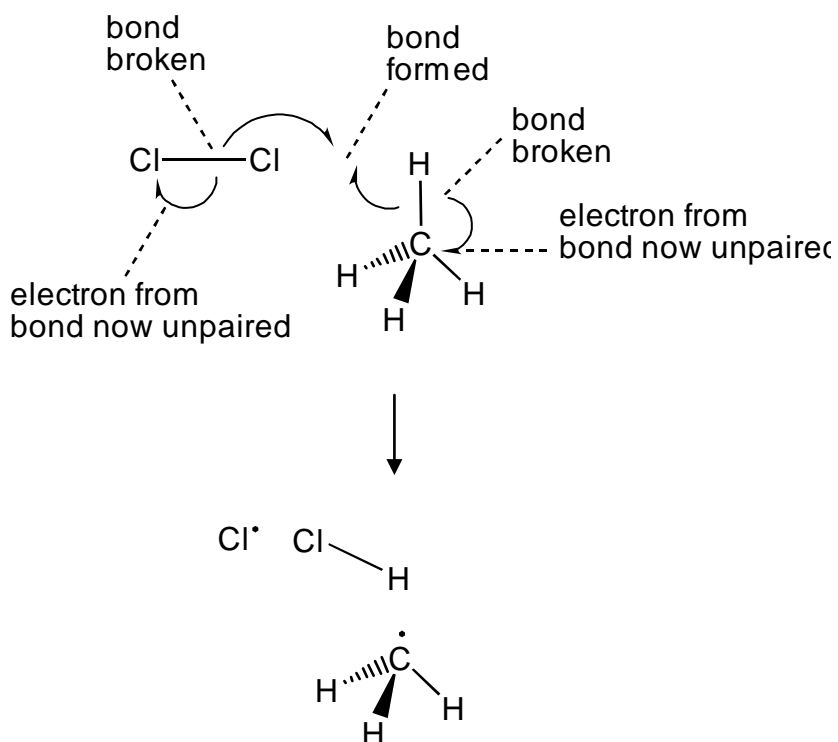
Reaction mechanism 1

The diagrams below show and explain the correct answer to the question about the ionic reaction mechanism.



Reaction mechanism 2

The diagrams below show and explain the correct answer to the question about the free radical mechanism.



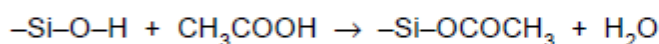
Gas chromatography (GC)

This technique uses a gas as the mobile phase, and the stationary phase can either be a solid or a non-volatile liquid (in which case small inert particles such as diatomaceous earth are coated with the liquid so that a large surface area exists for the solute to equilibrate with). If a solid stationary phase is used the technique is described as gas-solid adsorption chromatography, and if the stationary phase is liquid it is called gas-liquid partition chromatography. The latter is more commonly used, but in both cases the stationary phase is held in a narrow column in an oven and the stationary phase particles are coated onto the inside of the column.

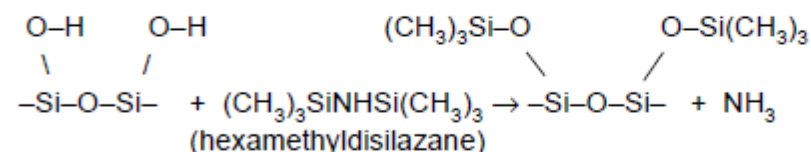
Diatomaceous earth is made from the skeletons of a single-celled non-flowering plant. The skeletons are made of hydrated silica, and are ground to a fine powder of the required particle size.

The advantage of diatomaceous earth is that it has fewer silanol (Si-OH) groups than silica and is less prone to electrostatic attractions (eg hydrogen bonds). The polarity of the OH groups can be reduced or eliminated by esterifying or silanising them.

Esterification with ethanoic acid:



Silanising:



Diatomaceous earth is also known as kieselguhr – the clay Nobel used as the inert base for dynamite.

Practical details

For separation or identification the sample must be either a gas or have an appreciable vapour pressure at the temperature of the column – it does not have to be room temperature. The sample is injected through a self sealing disc (a rubber septum) into a small heated chamber where it is vaporised if necessary (Fig. a). Although the sample must all go into the column as a gas, once it is there the temperature can be below the boiling point of the fractions as long as they have appreciable vapour pressures inside the column. This ensures that all the solutes pass through the column over a reasonable time span. The injector oven is usually 50–100 °C hotter than the start of the column. The sample is then taken through the column by an inert gas (known as the carrier gas) such as helium or nitrogen which must be dry to avoid interference from water molecules. It can be dried by passing it through anhydrous copper(II) sulphate or selfindicating silica (silica impregnated with cobalt(II) chloride). Unwanted organic solvent vapours can be removed by passing the gas through activated charcoal. The column is coiled so that it will fit into the thermostatically

controlled oven. The temperature of the oven is kept constant for a straightforward separation, but if there are a large number of solutes, or they have similar affinities for the stationary phase relative to the mobile phase, then it is common for the temperature of the column to be increased gradually over a required range.

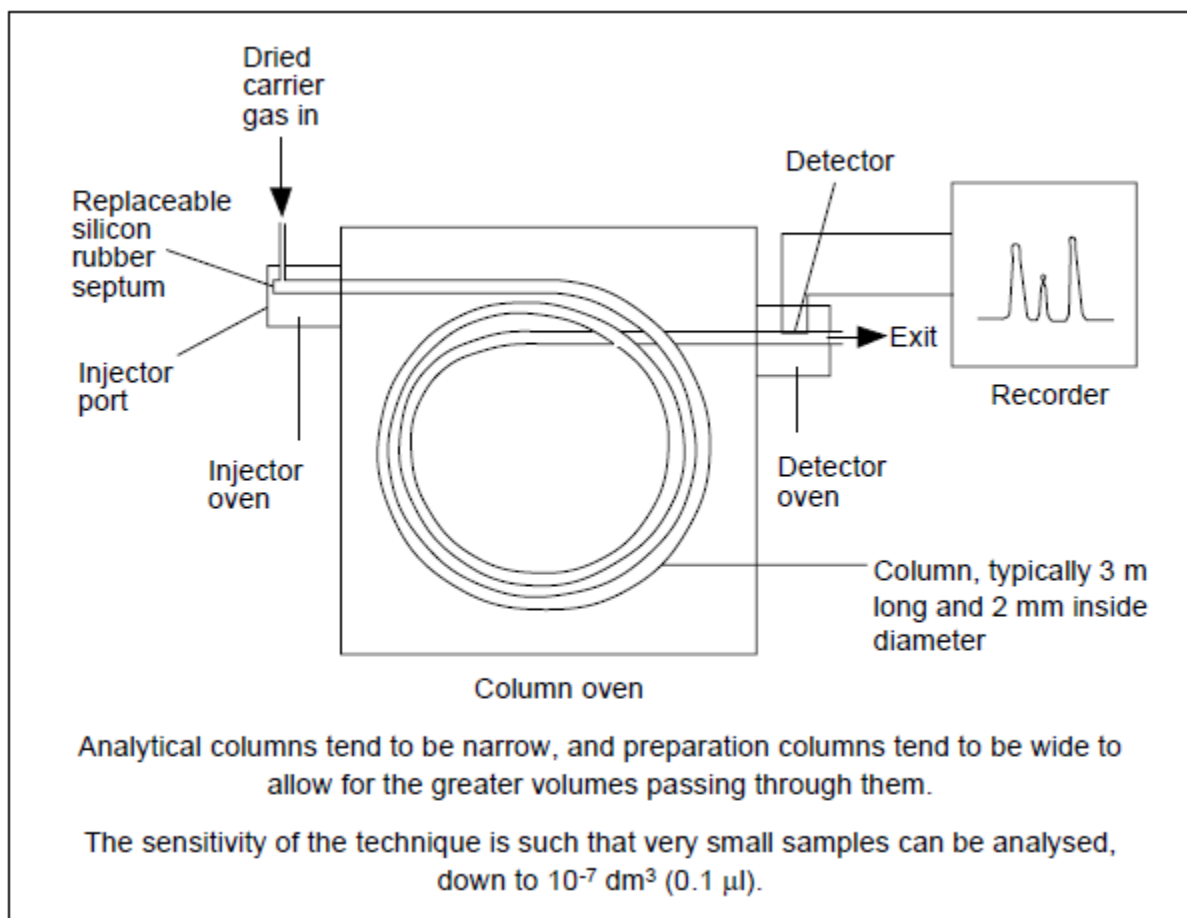


Figure a The Gas Chromatograph

This is done by using computer control, and gives a better separation if solute boiling points are close, and a faster separation if some components are relatively involatile. The solutes progress to the end of the column, to a detector. Two types of detector are commonly used: thermal conductivity detectors and flame ionisation detectors. Thermal conductivity detectors respond to changes in the thermal conductivity of the gas leaving the column. A hot tungsten–rhenium filament is kept in an oven set at a given temperature so that all solutes are in the gaseous phase (Fig. b). When the carrier gas – helium, for example, which will have been warmed to the temperature of the detector block – leaves the column it cools the hot filament. However, if a solute emerges with the helium it will cool the filament less (unless the solute is hydrogen, because only hydrogen has a thermal conductivity greater than helium) and the temperature of the filament will rise. Its resistance will then increase, and that can be measured.

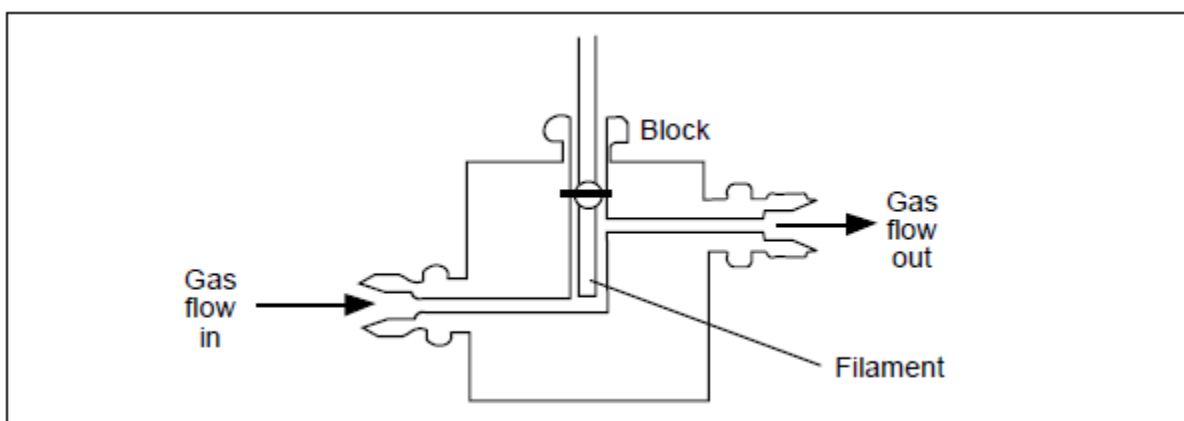


Figure b A Simple Thermoconductivity Detector

So that the change in resistance can be monitored directly a second circuit measures the resistance from the pure carrier gas.

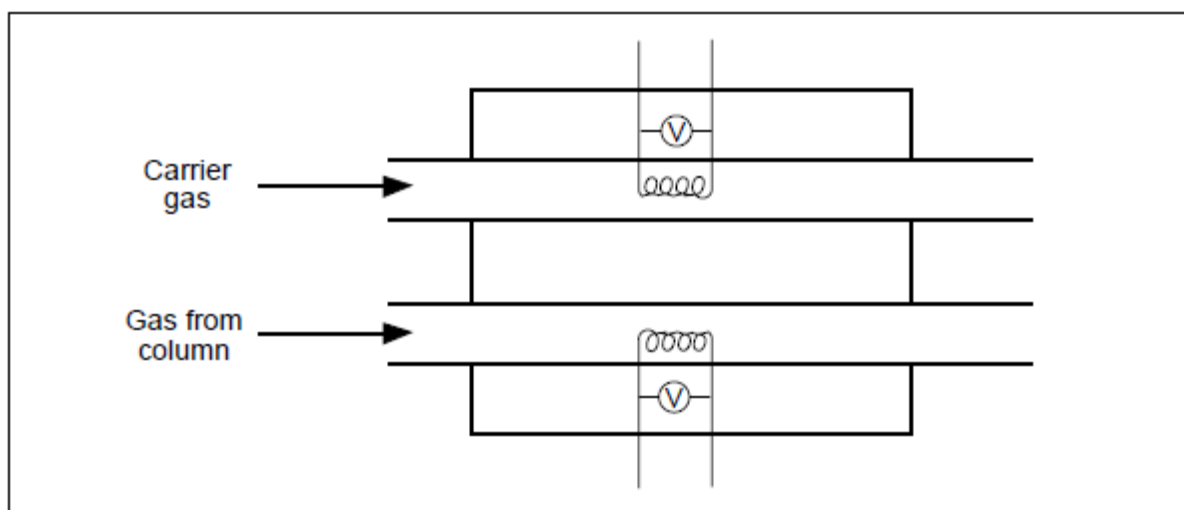
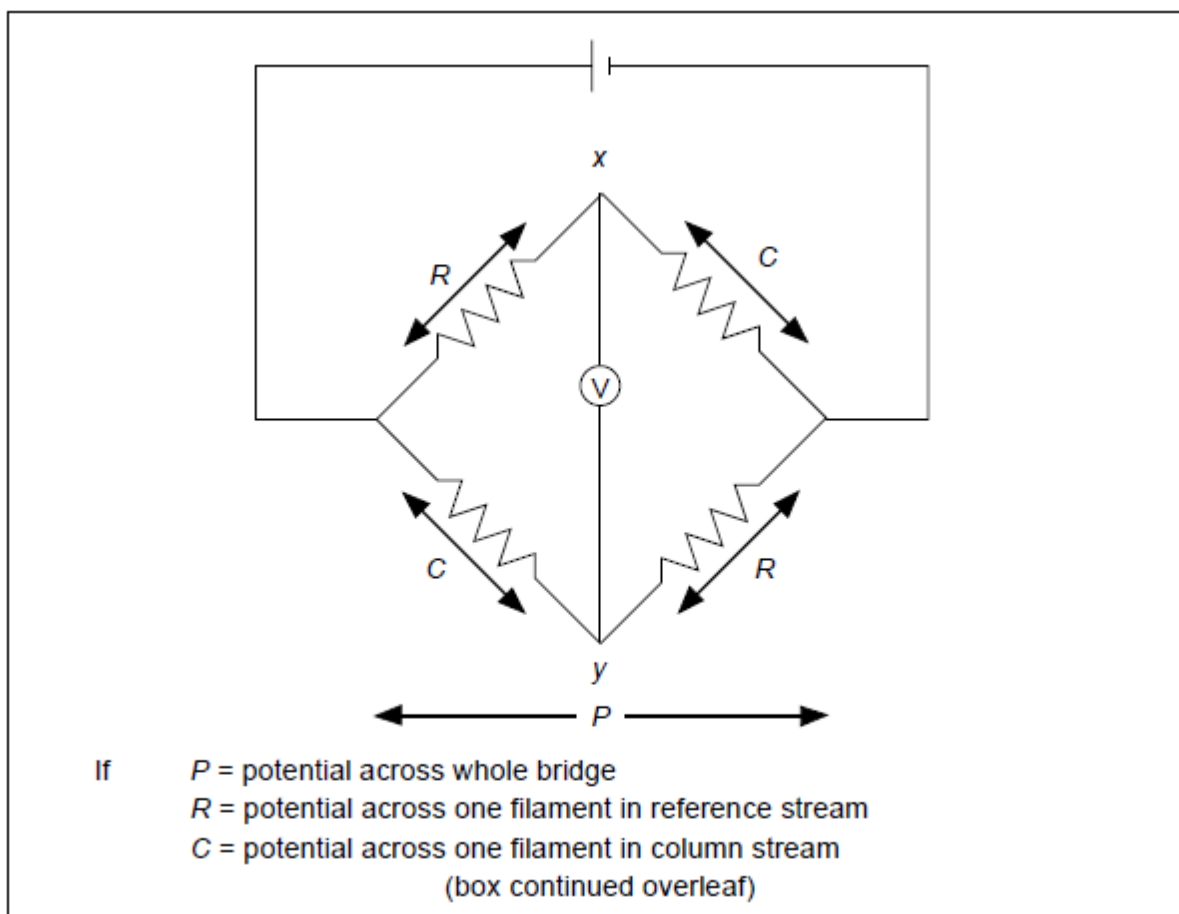


Figure c A Comparative Thermoconductivity Detector

The performance of a drug in vivo is frequently studied by using GC–MS. After giving volunteers a dose of the drug, blood plasma samples are taken at varying intervals, perhaps up to 24 h, and the parent drug and its metabolites are separated and identified. GC–MS has the advantage over other techniques that it is particularly sensitive – eg it can differentiate between the drug and its metabolites when their ultraviolet spectra are very similar. In reality, most thermal conductivity detectors have four filaments in a Wheatstone bridge arrangement, two filaments in the exit gas from the column and two in the reference gas stream (Fig. 12).



the potential at $x = \frac{R}{C+R} \times P$ potential at $y = \frac{C}{C+R} \times P$

therefore potential between x and y , measured on voltmeter, is

$$x-y = \frac{R-C}{C+R} \times P$$

If the gases in the two sides of the detector are the same, their conductivities will be the same so they will cool the filaments equally and $R-C=0$. The potential between x and y will then be zero. However, if the gases have different compositions then $R-C$ will not be zero and a value will be recorded.

Figure d Wheatstone Bridge arrangement of filaments

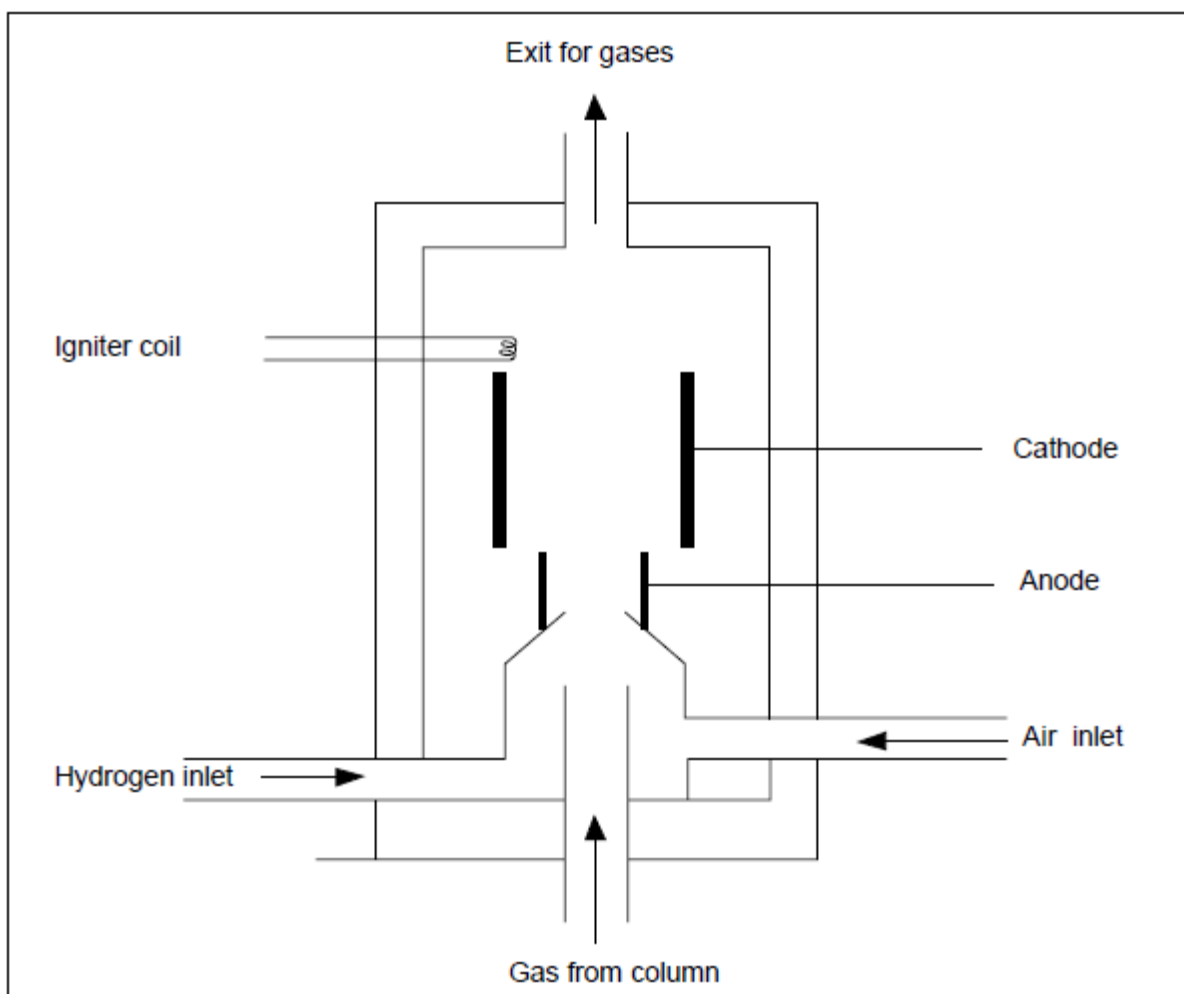


Figure e Flame Ionisation Detector

Although the number of ions produced is small (perhaps one in 10⁵ carbon atoms produce an ion) the proportion is constant. The current produced is also proportional to the number of ions produced, so the total signal on the chart peak is proportional to the amount of that solute in the mixture. A flame ionisation detector is approximately 1000 times as sensitive as the thermal conductivity detector for organic materials, but is of no use if the solutes do not burn or produce ions. Detectors are available that detect nitrogen and phosphorus as their ions, but these rely on excited rubidium atoms rather than a flame, to produce ions (see Fig f).

The nitrogen–phosphorus detector (NPD)

The NPD is fundamentally similar to the flame ionisation detector. They both work by forming ions and subsequently detecting them as a minute electrical current. However, a major difference arises in the way the ions are formed.

The eluate (exit gases) of the GC is forced through a jet in the presence of air and hydrogen gas. The mixture passes over the surface of a heated rubidium salt in the form of a bead. The excited rubidium atoms (Rb^*) selectively ionise nitrogen and phosphorus. The ions formed allow a small electric current to flow between two charged surfaces which, under different operating conditions, gives a response to either nitrogen or phosphorus containing compounds, or both (Fig. 14). To differentiate between nitrogen and phosphorus containing compounds the retention time of each solute in the column is used.

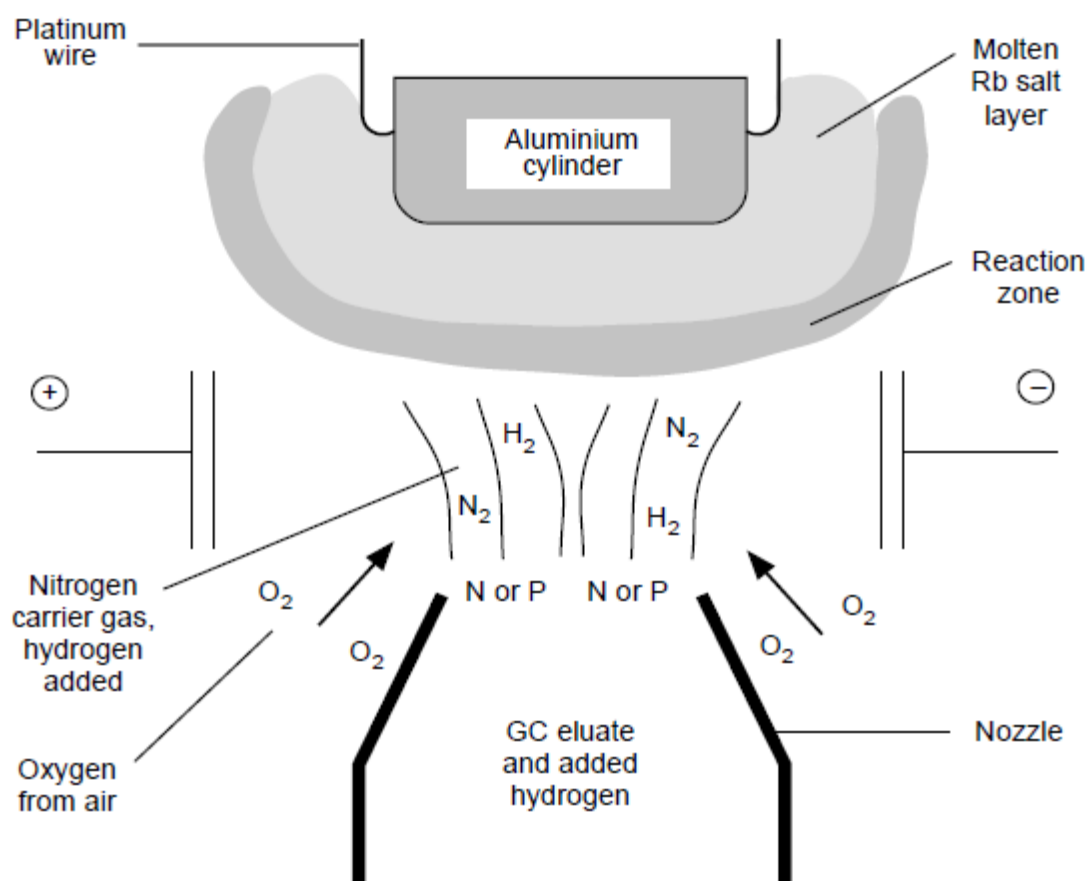


Diagram adapted by courtesy of Hewlett Packard

The rubidium bead is mounted on a small aluminium cylinder, and a current is supplied through a platinum wire (the current is a few pico amps). This current heats the bead and excites the rubidium atoms so that they can ionise nitrogen and phosphorus.

The hydrogen is used to maintain the temperature of the bead and consequently only a small flow rate is necessary (Table 1).

Table 1 Typical flow rates in the flame ionisation detector and the nitrogen–phosphorus detector /cm³ min⁻¹

	Air	Hydrogen
FID	300	30
NPD	100	4

The NPD can be set for phosphorus detection to determine very low concentrations of pesticides such as malathion, the active ingredient of Prioderm, a treatment used for killing head lice. The structure of malathion is:

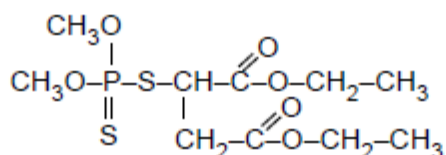


Figure f The Nitrogen-Phosphorous Detector

Once a mixture has been separated by GC its components need to be identified. For known substances this can be done from a knowledge of the time it takes for solutes to reach the detector once they have been injected into the column. These are known as retention times and will vary depending on each of the following:

- 1 the flow rate of the carrier gas;
- 2 the temperature of the column;
- 3 the length and diameter of the column;
- 4 the nature of and interactions between the solute and the stationary and mobile phases;
- 5 the volatility of the solute.

Each material to be identified by GC is run through the column so that its retention time (the time for the components to pass through the column) can be determined. For compounds of completely unknown structure or composition the solutes must be collected individually and then analysed by using another method – eg mass spectrometry.

The ideas of chromatography explored to date are further developed in this investigation of a model that illustrates the separation techniques employed in a more advanced technological techniques, gas chromatography.

Activity 7: Gas chromatography

Topic

Analytical techniques/separation of mixtures.

Timing

15 min or more.

Level

Post-16 or possibly pre-16.

Description

Volatile hydrocarbons are injected into a column containing washing powder. Natural gas is used as a carrier gas and burnt at a jet. The elution of the samples is detected by changes in the size and luminosity of this flame, which can be compared with a reference flame.

Apparatus

- One U-tube approximately 12 cm in length, with side arms .
- One rubber stopper to fit the U-tube mouth.
- One rubber septum cap to fit the U-tube mouth.
- Three 1 cm³ plastic syringes with hypodermic needles.
- One 1 dm³ beaker.
- Plastic and/or rubber tubing – see diagram.
- Glass funnel (optional).
- Stopclock.

Chemicals

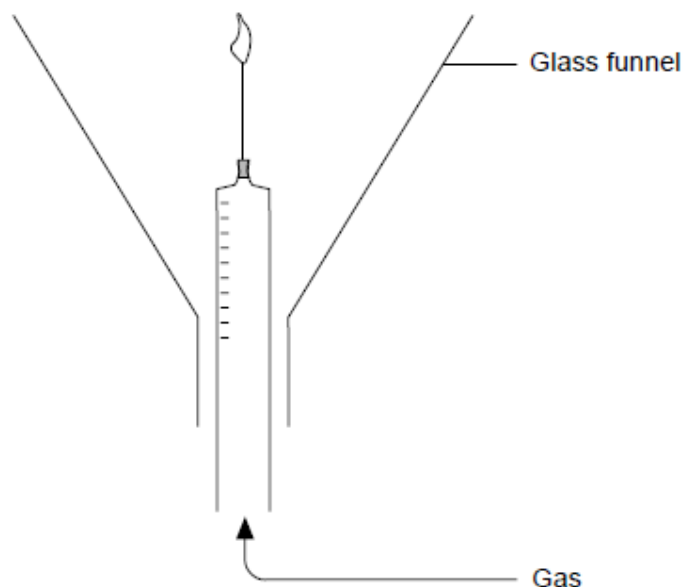
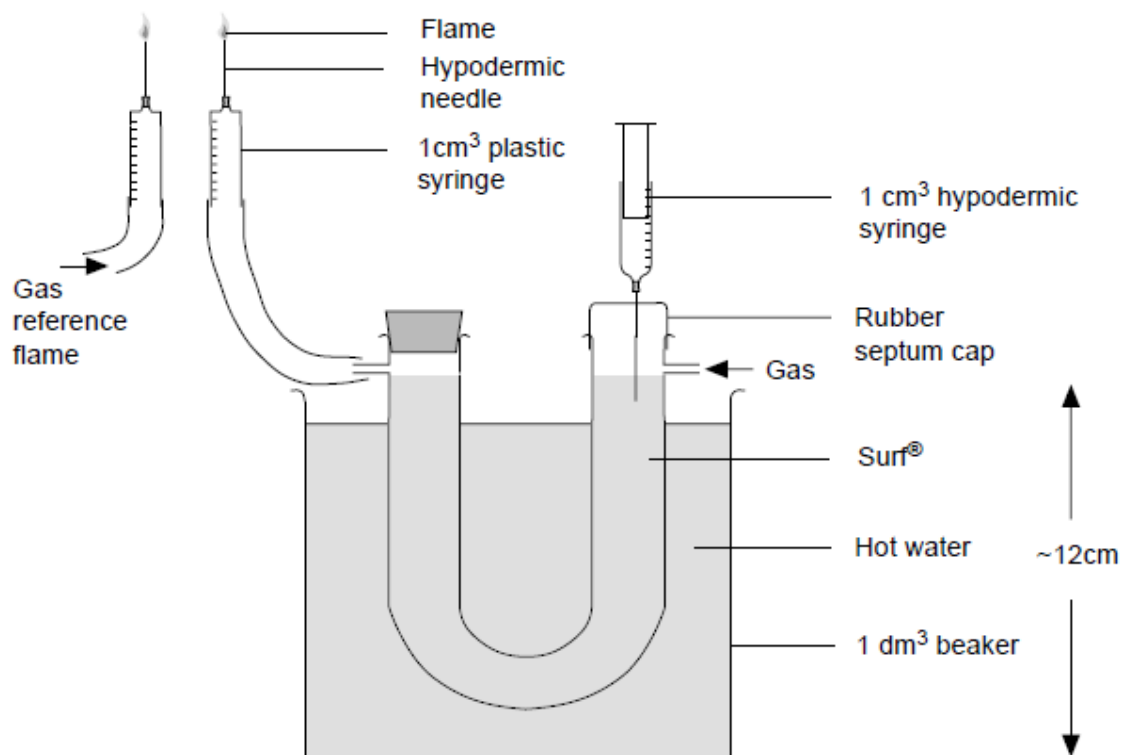
- A few cm³ of pentane (**extremely flammable, harmful, dangerous to the environment**) See CLEAPSS Hazcard 45A.
- A few cm³ of hexane. (**highly flammable, harmful, dangerous from the environment**) See CLEAPSS Hazcard 45A
- A few grams of Surf[®] washing powder.

Method

Before the demonstration

Dry the washing powder overnight in an oven. Fill the U-tube with washing powder to just below the level of the side arms. Stopper one mouth of the U-tube and fit a self-sealing rubber septum cap over the other. Connect one side arm to the gas tap with rubber tubing. The other side arm is connected with plastic or rubber tubing to a 1 cm³ plastic syringe which has had the handle end removed using scissors or a sharp

knife. Attach a hypodermic needle to the syringe and clamp this vertically to form a jet at which the gas can be burnt. Immerse the U-tube in a beaker full of water that has just boiled (see diagram below). Make a second jet with a cut-off syringe and hypodermic needle. Attach this by rubber tubing to a second gas tap. This will be used to provide a reference flame. Clamp this jet at the same height as, and close to, the first one.



Separation of gas mixtures

The demonstration

Wear eye protection.

Turn on the gas to the column and the reference jets. Light the jets and adjust them so that they have identical, almost non-luminous, flames about 2 mm high – screw clips on the gas tubes can help to achieve fine control. (It will take a short time for the air to be displaced from the column before the jet can be lit.) It may be necessary to improvise a draught shield to stop these small flames from going out. Take up about 0.02 cm³ of pentane in a hypodermic syringe. Insert the needle through the septum cap and into the Surf[®] and inject the pentane onto the column. Start the stopclock. Observe the flame carefully and note when it becomes significantly taller and more luminous than the reference flame. This will take roughly 40 seconds. Note also when the flame returns to normal (about 50 seconds later). Repeat this process with hexane instead of pentane. This will come through after about 80 seconds and affect the flame for about a further 70 seconds.

Visual tips

A black background seems to be best for observing the flames.

Teaching tips

After establishing the times for each compound to come through the column, try an 'unknown' – either hexane or pentane – and try to identify which it is. It is difficult to resolve a mixture reliably because the 'tail' of the pentane flame tends to mingle with the hexane one. Point out that real columns and detection systems can effect much better separations.

Theory

An equilibrium is set up between pentane adsorbed on the column material and that in the gas phase. Hexane is more strongly adsorbed on the column and is therefore carried more slowly by the carrier gas.

Extensions

Try heptane (**highly flammable, harmful, dangerous for the environment** – CLEAPSS Hazcard 45A). Try other compounds of similar volatility to pentane and hexane. Investigate the effect of the following variables: temperature, column length, column cross-sectional area, column filling material (kieselguhr works well, other washing powders could be used), volume of compound injected, gas flow rate etc.

Further details

One teacher involved in the trials reported that the following filling materials were all effective: Surf Micro[®], Radion[®], Ariel Ultra[®], Persil[®], acid washed sand (40–100 mesh), table salt. Retention times depend on the details of the apparatus and may differ from those reported here.

Glossary

adsorption	The adhesion of atoms or molecules to a surface.
affinity	The attraction of an analyte to a stationary phase.
analyte	The analyte is the substance to be separated during chromatography.
aromatic	Aromatic compounds are ring structures containing unsaturated bonds.
elutant	The solvent that carries the analyte.
ionisation	The process of conversion of an atom or molecule into an ion.
partition	The degree of separation of the components under chromatography.

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