Chemistry in your cupboard: Dettol

Introduction

One hundred and fifty years ago, before the use of antiseptics, major surgery often resulted in death from post-operative infections. In the 1860s Joseph Lister discovered phenol could kill germs but it also causes severe skin burns. Modern antiseptics such as Dettol® have been developed based on phenol but with modifications to the chemistry to reduce the adverse effects and produce a safer product. Many antiseptics are still made based on phenol derivatives as the active ingredient.

Links to the curriculum

This section contains information relevant to the following areas of your chemistry curriculum:

- Organic chemistry
- Bonding
- Acids and bases

DETTOL

Antiseptics and disinfectants

Before the mid-1800s, major surgery was often a death sentence. Amputations of damaged limbs were carried out as a last resort but patients frequently died from post-operative infections.

This changed in the 1860s when Joseph Lister developed antiseptic surgery using carbolic acid to sterilise wounds and instruments. Lister was aware of the germ theory of infections developed by Louis Pasteur and others, and knew that carbolic acid (which we now call phenol) was able to kill germs, Figure 1.

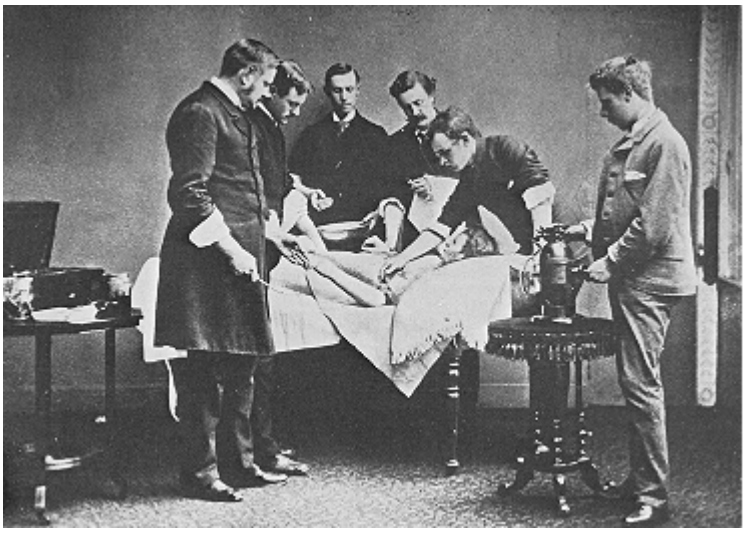


Figure 1: An operation in the 1870s. Doctors are using a carbolic acid spray as an antiseptic. Notice that they appear to be wearing their everyday clothes! (Wellcome Photo Library, Wellcome Images)

It is reputed that phenol's germ-killing power first came to notice in a bizarre way. Sailors who underwent amputations at sea appeared to have a higher survival rate than patients in hospital. This seemed to be due to the practice at sea of dipping the stump into molten tar to seal the wound. Tar contains, among other things, phenol, Figure 2.

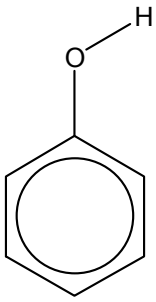


Figure 2: Structure of phenol.

Nowadays, disinfectants are just as important for germ-killing in hospitals, homes and elsewhere. Many products are still based on phenol derivatives as the active ingredient. This site looks at Dettol, made by Reckitt Benckiser.

Structure activity relationships

Phenol is effective at killing germs but is otherwise a far from ideal antiseptic as it causes nasty skin burns. One technique used by pharmaceutical chemists when faced with this sort of situation is to synthesise a number of compounds related to the substance that is known to be effective. This is in the hope that one or more of these compounds will be as active, or better, than the original but with fewer side effects (such

as skin burning). Even better is the possibility of establishing a structure-activity relationship. This is a pattern which links some structural feature of the molecule with its pharmacological efficiency (ie how effective it is as a medicine) in a systematic way. Examples of such a relationship could be that

- the more methyl groups attached to a benzene ring, the better the germ-killing power, or
- the more electronegative a substituent, the less harmful to the skin.

This enables the chemist to predict which derivatives might be more effective and therefore guide the synthesis of new compounds. Figure 3 shows some derivatives of phenol along with their germ-killing power relative to phenol. All of the compounds (except phenol itself) are substituted phenols. That is the new group or groups attached to the benzene ring replace one or more of the hydrogens.

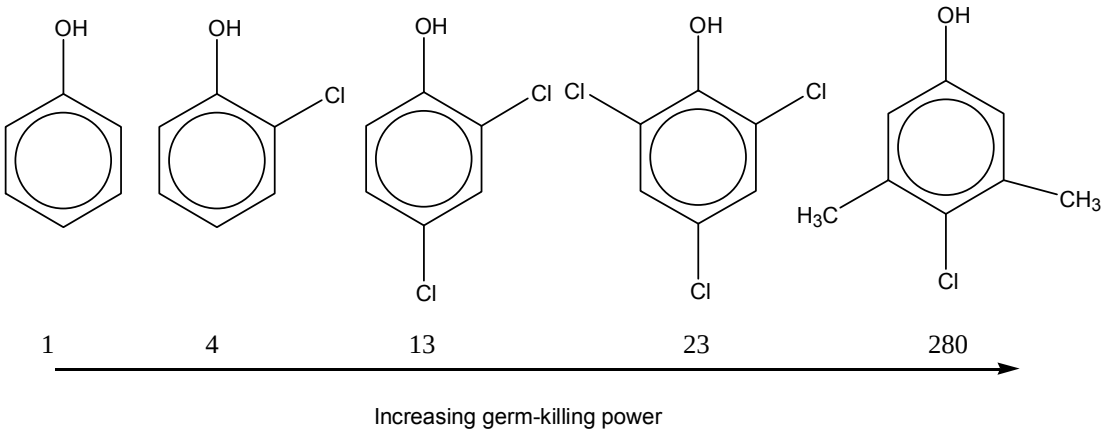


Figure 3: The relative germ-killing power of some substituted phenols.

Question 1
What sort of structure-activity relationship is suggested by the first four compounds in Figure 3? Suggest what other compounds might be synthesised to check this hypothesis.

Question 2
The first compound in Figure 3 is phenol and the last is called 4-chloro-3,5-dimethylphenol. Name the other three.

Question 3

a) The benzene ring is often drawn as in Figure 3. There is a hydrogen atom (not drawn) at each 'corner' of the hexagon unless there is another atom or group attached. The circle represents a delocalised ring of electrons in a π orbital above and below the ring – this is called an aromatic system.

Explain why compounds with an aromatic ring invariably form substituted derivatives rather than addition compounds.

b) State and explain what type of reagents is most likely to attack aromatic rings.

In fact the structure-activity relationships that have been established for derivatives of phenol are:

- the −OH group is required for activity;
- activity increases with a halogen in the 4- position (ie opposite the −OH group in the ring);
- activity increases with alkyl substituents of increased chain length;
- increased substitution makes the compound less water-soluble; and
- increased substitution decreases toxicity to humans when taken by mouth.

Phenol is already an effective germicide, so a greater killing power is not really needed. What the greater efficiency of 4-chloro-3,5-dimethylphenol means is that much smaller concentration can be used and therefore fewer side-effects will be expected.

Dettol

The active germ-killing ingredient in Dettol is in fact 4-chloro-3,5-dimethylphenol, also known by its non-systematic name *para*-chloro-*meta*-xylenol or PCMX, Figure 4. The prefix *para* is a non-systematic way of indicating the 4- position on the benzene ring, ie opposite the −OH group. *Meta* indicates the 3- and 5- positions.

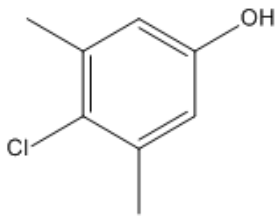


Figure 4: Structure of *para*-chloro-*meta*-xylenol or PCMX.

A number of disinfectant and antiseptic products are available under the Dettol brand including disinfectants for surfaces, antiseptics for use on the body, wipes and sprays. Here we will concentrate on the 'core' product - the liquid antiseptic, Figure 5.

Always read the label

Figure 5: Dettol liquid antiseptic, contains chloroxylenol.

Biocides, disinfectants and antiseptics

All the terms above refer to germ (ie microbe)-killing. Biocide is a general term which covers active ingredients that kill microbes. Disinfectants kill microbes (bacteria, fungi and viruses) and are used on surfaces (such as worktops, sinks etc) but not living things (such as skin) as they may harm them. Antiseptics also kill microorganisms but may be used on the body surface (skin) although not in the body (eg by mouth).

How does PCMX kill bacteria?

The detailed biochemistry of the action of PCMX and other phenol-based antibacterial agents is beyond the scope of this site. However, very simply, they are understood to work by the −OH group of the molecule binding to proteins present on the cell membrane of bacteria, disrupting the cell membrane and allowing the contents of the cell to leak out.

This allows more PCMX to enter the cell, binding further with proteins and enzymes, and effectively shutting down the cell's functions. At high concentrations of PCMX, the proteins and nucleic acids in the cell are coagulated and cease to function, leading to rapid cell death.

The acidity of phenols (1 of 3)

Phenol, C_6H_5OH, is weakly acidic - it was once called carbolic acid (not to be confused with carbo*xylic* acids, which contain the group −COOH). The acidic hydrogen (the one that is lost as H^+ when phenol behaves as an acid) is the hydrogen of the −O-H group. This is because oxygen is much more electronegative than hydrogen (3.5 on the Pauling scale compared with 2.1) so the O-H bond is polarised $O^{\delta-}$-$H^{\delta+}$, making it relatively easy for this hydrogen to be lost as a proton (H^+ ion), Figure 6.

The negative ion formed is called the phenoxide ion and is often represented in text as PhO^-, Ph, being used to represent a benzene ring, which is sometimes called the phenyl group. Because it is ionic, the phenoxide ion is more soluble in water than phenol itself.

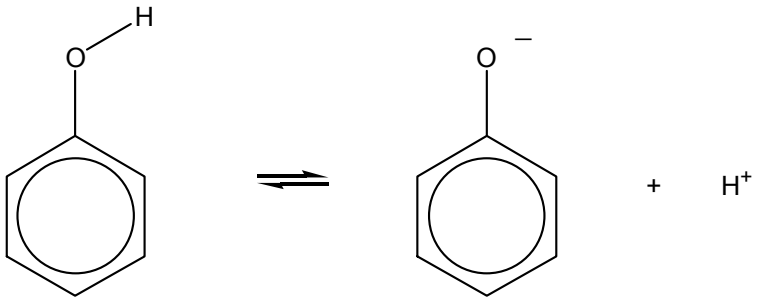


Figure 6: Phenol, is also weakly basic – the oxygen atom has two lone pairs, one of which can accept a H^+ ion to form the ion $PHOH_2^+$.

The pK_a value is a measure of the strength of an acid (how easily a H^+ ion is lost). The larger the pK_a value, the weaker the acid.

- PCMX pK_a = 9.7; $K_a = 1.99 \times 10^{-10}$ mol dm^{-3}
- phenol pK_a = 9.9; $K_a = 1.28 \times 10^{-10}$ mol dm^{-3}
- ethanol pK_a = 15.9; $K_a = 7.9 \times 10^{-15}$ mol dm^{-3}

The acidity of phenols (2 of 3)

Imagine a weak acid, HA, which dissociates

$$HA_{(aq)} \rightleftharpoons H^+_{(aq)} + A^-_{(aq)}$$

The equilibrium constant is given by:

$$K_c = \frac{[H^+(aq)]_{eqm}[A^-(aq)]_{eqm}}{[HA_{(aq)}]_{eqm}}$$

For a weak acid, this is usually given the symbol K_a and called the acid dissociation constant**.**

$$K_a = \frac{[H^+(aq)]_{eqm}[A^-(aq)]_{eqm}}{[HA_{(aq)}]_{eqm}}$$

$pK_a = -\log_{10} K_a$

(This is analogous with $pH = -\log_{10}[H^+]$)

The larger the value of K_a, the stronger the acid (the greater $[H^+]$ it produces on dissociation). However, because of the **−** sign in the expression above, the larger the value of pK_a, the *weaker* the acid.

Question 4

The solubility of PCMX is 330 mg dm^{-3} and its K_a is 1.99×10^{-10}. Calculate the pH of a saturated solution of PCMX.

The acidity of phenols (3 of 3)

Why is phenol so much more acidic than ethanol? In other words, why is the H of the OH group of ethanol so much less likely to be lost than that of the OH group of phenol?

$$C_2H_5OH \rightleftharpoons C_2H_5O^- + H^+$$

The answer lies in the relative stabilities of the negative ions left after a H^+ ion has been lost. In the ethoxide ion, the charge remains localised on the oxygen atom. In the phenoxide ion, PhO^-, the negative charge is spread over the benzene ring due to overlap of a p-orbital on the oxygen atom with the delocalised π-system of the benzene ring, Figure 7.

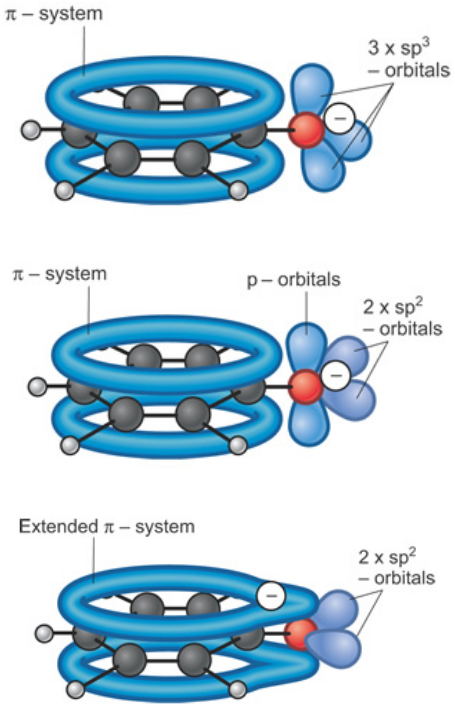


Figure 7: Delocalisation in the phenoxide ion.

In the top diagram, the oxygen atom is shown hybridised sp^3 (see next page) with a pair of electrons in each of the three blue orbitals. (The fourth sp^3-orbital is involved in forming a σ-bond with the carbon atom on the ring to which it is attached.) In the middle diagram, the oxygen atom is shown hybridised sp^2 with the p-orbital vertical ready to overlap with the aromatic system. In the bottom diagram, the oxygen atom is hybridised sp^2, its unhybridised p-orbital has overlapped with the 'doughnut-shaped' delocalised orbital of the benzene ring and the negative charge is spread over the ring.

Hybridisation

Hybridisation is a concept used to help explain the shapes of molecules. It is based on the idea that any atom, orbitals of similar energy such as 2s and 2p can 'mix together' to

produce the same number of new orbitals of a different shape. These hybrid orbitals can then form bonds by overlapping with orbitals on other atoms.

For example in carbon, oxygen and nitrogen, where the orbitals involved in bonding are the 2s and 2p-orbitals, they may mix in three ways.

1. $s + 3 \times p \rightarrow 2 \times sp + 2 \times p$
2. $s + 3 \times p \rightarrow 3 \times sp^2 + 1 \times p$
3. $s + 3 \times p \rightarrow 4 \times sp^3$

The notation sp, sp^2 and sp^3 gives the proportion of s and p orbitals in the hybrid. For example, an sp^3 is ¼ s and ¾ p. Notice that the original four orbitals always give rise to four new ones. The shapes are shown in Figure 8.

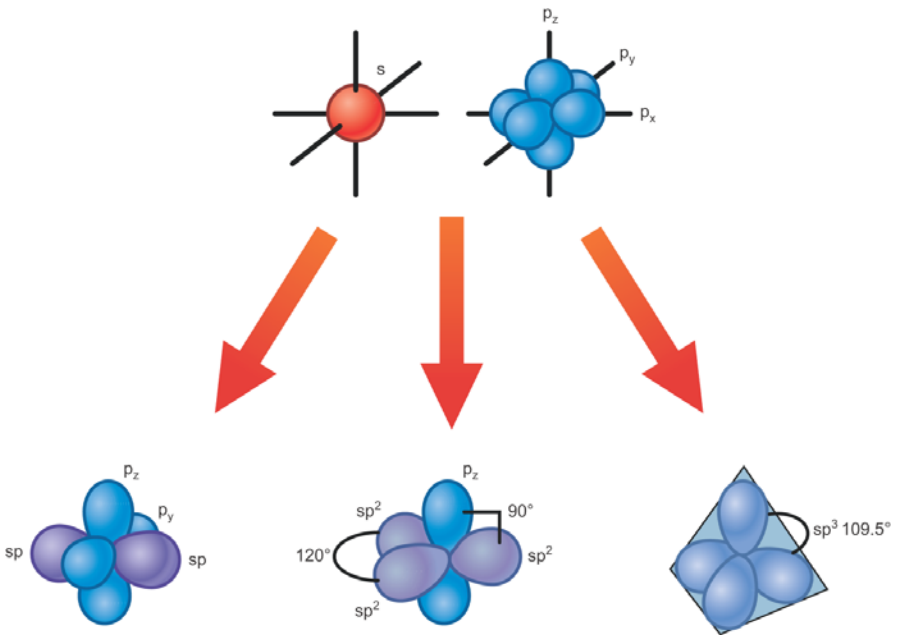


Figure 8: Formation of hybrid orbitals - the three possibilities.

The angles between the hybridised orbitals are important as they help to explain the shapes of molecules. The sp orbitals are at 180° to one another, the sp^2 at 120° and the sp^3 point to the corners of a tetrahedron (109.5°).

Hint sp^2 is pronounced 'ess pee two' not 'ess pee squared'.

Making the active ingredient soluble (1 of 3)

PCMX is, as expected, not very soluble in water; only 330 mg dm^{-3}.

Question 5
Why would you expect PCMX to be relatively insoluble in water?

This is because only the –O-H group can form hydrogen bonds with water.

Question 6
Draw a diagram to show how a water molecule can form a hydrogen bond with a phenol molecule
a) via a hydrogen atom on the water.
b) via an oxygen atom on the water.

Because they are acidic, phenols and substituted phenols are more soluble in alkaline solutions. However, strongly alkaline solutions are caustic and damage the skin so a slightly alkaline solution, pH 10, is used. In fact, PCMX shows slightly less activity at pH 10 than in a neutral solution.

Dettol actually contains 4.8% w/v PCMX.

w/v stands for weight per unit volume, so this is 4.8 g in 1000 cm^3 or 48 g dm^{-3} (48,000 mg dm^{-3}), nearly 150 times as much as its solubility in pure water. How is this achieved?

PCMX is soluble in relatively non-polar solvents - one such is pine oil which is used in the formulation of Dettol. This oil is derived, not surprisingly, from needles, twigs and cones of pine trees. Pine oil is a mixture composed largely of *alpha*-terpineol, which is moderately polar because of its single –OH group, Figure 9.

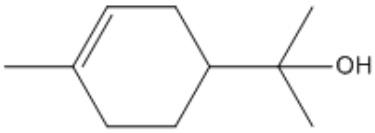


Figure 9: Structure of *alpha*-terpineol.

The rest of the pine oil consists largely of hydrocarbons. It contains terpenes, a group of hydrocarbons which are essentially polymers of isoprene, Figure 10.

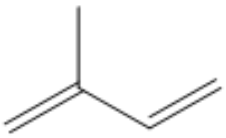


Figure 10: Structure of isoprene.

Question 8

- **What is the molecular formula of isoprene?**
- **What is the empirical formula of isoprene?**

Question 9
What is the systematic name of isoprene?

Making the active ingredient soluble (2 of 3)

The answer to increasing the solubility of PCMX is to use a soap.

Soaps and detergents have 'tadpole-shaped' molecules in that they have a non-polar 'tail' and a polar or ionic 'head'. The 'tail' can form van der Waals bonds with non-polar molecules whilst the 'head' can form hydrogen bonds with water. This is an example of the 'like dissolves like' rule.

The soap used in Dettol is made from castor oil which contains ricinoleic acid (systematic name 12-hydroxy-(*cis*)-9-octadecenoic acid), Figure 11.

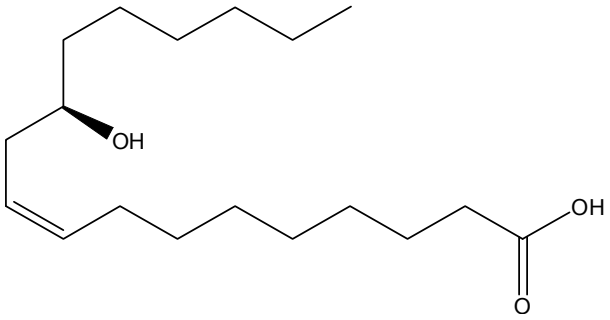


Figure 11: Structure of ricinoleic acid.

Question 10
Explain the systematic name 12-hydroxy-(*cis*)-9-octadecenoic acid.

Historically, the positions of substituents around double bonds have been indicated by the terms *cis* (on the same side) and *trans* (on the opposite side).

An alternative notation makes it possible to deal with more complex cases. The E-Z notation is based on atomic numbers. We look at the atoms attached to each of the carbon atoms in the double bond. When the two atoms (of each pair) of higher atomic number are on the same side of the C=C, the isomer is described as Z, from the German word for together, *zusammen*. If not it is E, from the German word for opposite, *entgegen*.

So, if the two atoms with the greatest atomic number are on the *same* side of the double bond as in ricinoleic acid, the configuration is Z.

Making the active ingredient soluble (3 of 3)

The ricinoleic acid is reacted with sodium hydroxide to form the ionic salt sodium ricinoleate. This salt has an ionic head and a largely non-polar tail – the classic shape of a detergent or surfactant molecule, see Figure 12.

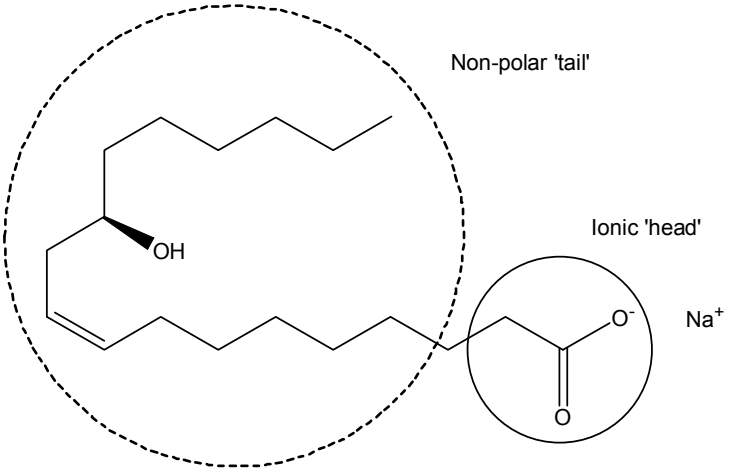


Figure 12: Structure of sodium ricinoleate.

In the bottle, Dettol consists of an almost clear liquid in which the PCMX is held in solution by the sodium ricinoleate.

On dilution in water, however, a cloudy liquid forms. This consists of droplets of pine oil containing dissolved PCMX. These are held dispersed in water by a layer of soap molecules arranged with their tails in the pine oil and their heads in the water, Figure 13. These droplets are big enough to scatter light, hence the cloudiness of the suspension which is called an emulsion.

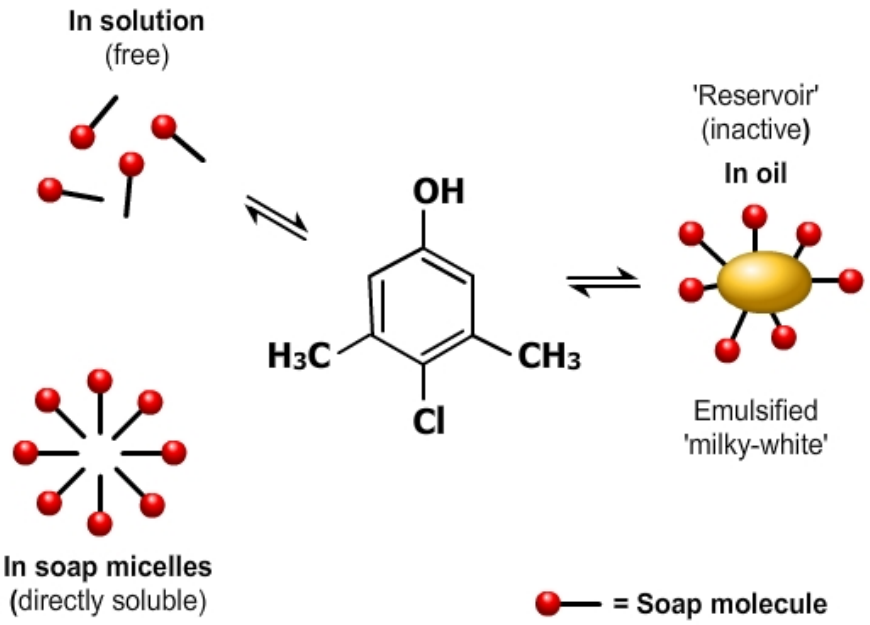


Figure 13: PCMX in aqueous solution exists in a number of forms.

The PCMX in the droplets of pine oil is not available to kill bacteria - it is the free aqueous PCMX that does this. However, an equilibrium exists between the emulsified PCMX in the droplets and free PCMX dissolved in the water. As PCMX is used up in killing bacteria, more is released from the droplets to keep the aqueous PCMX concentration essentially constant. So the droplets act as a reservoir of PCMX.

Question 11
What chemical principle predicts that as the aqueous PCMX is used up, more will dissolve from the droplets and the micelles to maintain its concentration?

There is a further reservoir of PCMX in so-called micelles. These are groups of soap molecules clustered together with their non-polar tails entwined. Non-polar PCMX molecules can exist inside these micelles and be released in a similar way to those in the droplets. Also in solution are free soap molecules which in fact aid the penetration of PCMX into the bacterial cell walls. In addition, pine oil itself has a mild antibacterial action.

Pine oil also has a pleasant smell of pine and over the years, this has become associated in the mind of the public with antiseptic and disinfectant action, so much so that most disinfectant products are formulated with a pine smell.

Although improvements have been made over the years, the basic formulation of Dettol and similar products has remained the same since the 1930s.

Other ingredients and formulations

There are a number of other ingredients in the formulation of Dettol including propan-2-ol (*iso*propanol), Figure 14.

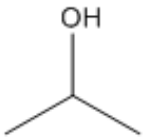


Figure 14: Structure of propan-2-ol (*iso*propanol).

This helps to make the PCMX soluble in water and helps to stabilise the micelles. Caramel gives the product its yellow-brown colour.

As well as Dettol liquid antiseptic, Dettol branded products are sold in a number of other forms with different formulations. Most of the Dettol products are not medicines and therefore do not have registered actives, Figure 15.

Figure 15: Different forms and formulations of products sold under the Dettol brand.

Further information

Dettol is sold in the UK by Reckitt Benckiser (www.dettol.co.uk). There are other branded products which work in a similar way.

Acknowledgements

The Royal Society of Chemistry wishes to thank Reckitt Benckiser for help in preparing this material.

The Royal Society of Chemistry gratefully acknowledges that this project was initially supported by Reckitt Benckiser in 2007. Reckitt Benckiser conducted a final review in 2013 so please note that certain information may be out of date.

QUESTIONS AND ANSWERS

Question 1
What sort of structure-activity relationship is suggested by the first four compounds in Figure 3? Suggest what other compounds might be synthesised to check this hypothesis.
It suggests that the more chlorine substituents, the greater the germ-killing activity. More highly-substituted derivatives could be made, such as 2,3,4,5-tetrachlorophenol.

Question 2
The first compound in Figure 3 is phenol and the last is called 4-chloro-3,5-dimethylphenol. Name the other three.
2-chlorophenol; 2,4-dichlorophenol; 2,4,6-trichlorophenol.

Question 3
a) The benzene ring is often drawn as in Figure 3. There is a hydrogen atom (not drawn) at each 'corner' of the hexagon unless there is another atom or group attached. The circle represents a delocalised ring of electrons in a π orbital above and below the ring – this is called an aromatic system.

Explain why compounds with an aromatic ring invariably form substituted derivatives rather than addition compounds.
Aromatic compound are more stable than expected due to the delocalised ring of six electrons. Forming addition products would require one or more of these electrons to be used in forming bond(s) with added group(s) and therefore destroy the aromatic stability.

b) State and explain what type of reagents is most likely to attack aromatic rings.
Electrophiles. These attack the high electron-density of the delocalised system of electrons.

Question 4
The solubility of PCMX is 330 mg dm^{-3} and its K_a is 1.99 x 10^{-10}. Calculate the pH of a saturated solution of PCMX.

$$K_a = \frac{[H^+_{(aq)}]_{eqm}[A^-_{(aq)}]_{eqm}}{[HA_{(aq)}]_{eqm}}$$

330 mg = 0.33 g

0.33 / 156.6 mol = 2.11 x 10^{-3} mol in 1 dm^3

ie the initial concentration of PCMX, $[PCMX_{(aq)}]$ = 2.11 x 10^{-3} mol dm^{-3}.

$PCMX \rightarrow H^+ + PCMX^-$

$$1.99 \times 10^{-10} = \frac{[H^+_{(aq)}]_{eqm}[PCMX^-_{(aq)}]_{eqm}}{[PCMX_{(aq)}]_{eqm}}$$

Since some PCMX dissociates, $[PCMX_{(aq)}]_{eqm} = [PCMX_{(aq)}] - [H^+_{(aq)}]_{eqm}$

$$\text{So } 1.99 \times 10^{-10} = \frac{[H^+_{(aq)}]_{eqm}[PCMX^-_{(aq)}]_{eqm}}{[PCMX_{(aq)}]_{eqm} - [H^+_{(aq)}]_{eqm}}$$

Since $[H^+_{(aq)}]_{eqm} = [PCMX^-_{(aq)}]_{eqm}$ and $[H^+_{(aq)}]_{eqm}$ is small

$$1.99 \times 10^{-10} = \frac{[H^+_{(aq)}]^2_{eqm}}{[PCMX_{(aq)}]_{eqm}}$$

$$1.99 \times 10^{-10} = \frac{[H^+_{(aq)}]^2_{eqm}}{2.11 \times 10^{-3}}$$

$[H^+_{(aq)}]^2_{eqm} = 4.2 \times 10^{-13}$

$[H^+_{(aq)}]_{eqm} = 6.48 \times 10^{-7}$ mol dm^{-3}

$pH = -\log_{10}[H^+] = 6.19$

Question 5

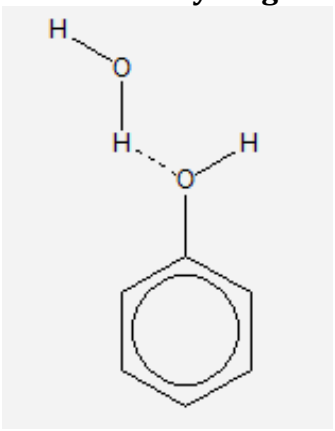
Why would you expect PCMX to be relatively insoluble in water?

The only polar part of the molecule which can hydrogen bond to water molecules is the OH group, the rest is non-polar and unable to interact strongly with polar water molecules.

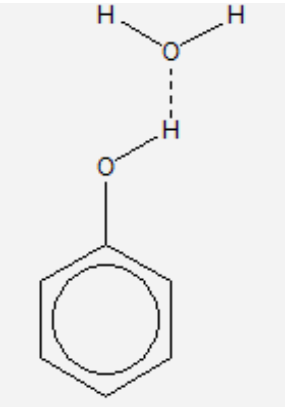
Question 6

Draw a diagram to show how a water molecule can form a hydrogen bond with a phenol molecule

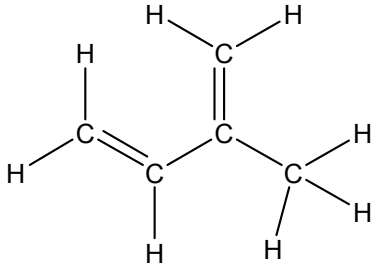
- **via a hydrogen atom on the water**



- **via an oxygen atom on the water**



Question 7
Write out the structural formula of isoprene using a displayed formula



Question 8

- **What is the molecular formula of isoprene?**
- **What is the empirical formula of isoprene?**
- C_5H_8
- C_5H_8

Question 9
What is the systematic name of isoprene?
2-methylbuta-1,3-diene

Question 10
Explain the systematic name 12-hydroxy-(*cis*)-9-octadecenoic acid.

- octadec indicates that there are 18 carbon atoms
- oic acid indicates a carboxylic acid (COOH) functional group
- ene indicates an alkene, a carbon-carbon double bond (C=C)
- the 9 indicates the position of the C=C between carbons 9 and 10 (counting from the COOH end of the molecule)
- hydroxy indicates an alcohol (OH) functional group
- the 12 indicates that the OH group is on carbon 12 (counting from the COOH end of the molecule)
- *cis* indicates that both chains attached to the C=C are on the same side

Question 11
What chemical principle predicts that as the aqueous PCMX is used up, more will dissolve from the droplets and the micelles to maintain its concentration?
Le Chatelier's principle.