Acidity of alcohols continued …

What is the influence of substituents? inductive & resonance

As the $pK_a$ values above show, phenol is $10^8$ more acidic than cyclohexanol.

Phenol has a $pK_a$ value of 10 (given this information, you should immediately recognize that it is more much acidic (about 6 orders of magnitude) than water ($pK_a$ 15.7) and methanol ($pK_a$ 16) since it has lower $pK_a$ value). As phenol is more acidic, this means that its conjugate anion is more stable. The phenoxide anion is stabilized through resonance (shown above). It has 4 resonance forms, and therefore, more ability to spread the negative charge and be stabilized.

Where does the equilibrium lie for ionization of phenol to phenoxide and a proton ($H^+$)?

Answer: It lies far to the left (not ionized). Even though phenol is $10^6$ more acidic than water, its $pK_a$ of 10 tells you that the acidity constant is $10^{-10}$ or that only one part in $10^{10}$ is ionized, the rest exists as phenol with H attached to oxygen.
Example: Chlorophenol (Above)

Is the anion more or less stabilized compared to phenol?

Answer: more stabilized. The chlorine atom is electron withdrawing, and stabilizes the negative charge at the para position through the inductive withdrawing effect. However, it also has a weak resonance donating effect. The inductive effect of chlorine wins over resonance effect in this case (contrast this with electrophilic aromatic substitution where the resonance donating effect wins out against the inductive effect).

Example:

\[
\text{m-nitrophenol} \quad \text{v.s} \quad \text{p-nitrophenol}
\]

\(m\)-nitrophenol has a pK\(_a\) value of 9.3, whereas the \(p\)-nitrophenol has pK\(_a\) value is 7.2.

*Which one is more acidic?*

Answer: \(p\)-nitrophenol

Why? (Think about conjugate anion stabilization and resonance forms).
Resonance forms for \textit{m}-nitrophenoxide anion:

\begin{center}
\includegraphics[width=\textwidth]{m-nitrophenoxide_resonance}
\end{center}

Resonance forms for \textit{p}-nitrophenoxide anion:

\begin{center}
\includegraphics[width=\textwidth]{p-nitrophenoxide_resonance}
\end{center}

The nitro group offers an additional resonance form for \textit{p}-nitrophenol that is not possible for \textit{m}-nitrophenol (we are able to drive electrons all the way in to the nitro group for the \textit{para}-substituted nitrophenol). Since there is one more reasonable resonance form, the \textit{p}-nitrophenol \( pK_a \) 7.2 is about 100 times \( 10^2 \) more acidic than the \textit{m}-nitrophenol with \( pK_a \) 9.3 (\( pK_a \) 9.3-7.2 = 2.1 \( pK_a \) units)

If there are two nitro groups in the \textit{ortho} and \textit{para} positions of the phenoxide anion, the \( pK_a \) of the phenol (2,4-dinitrophenol) drops to 4.5. If three nitro groups are attached, the \( pK_a \) of the phenol becomes even lower (2,4,6-trinitrophenol has a \( pK_a \) of approximately 0.5). This is because \textit{ortho} and \textit{para} positions are where the negative charge of the resonance form can be located, and addition of a nitro group is able to offer more stabilization. This phenomenon is not observed for the \textit{meta} position.

\textbf{Ethers}

An ether is a substance that has two organic groups bonded to the same oxygen atom, R-O-R', where R and R' can be the same or different, but cannot be carbonyl (C=O), or H directly attached. The organic groups may be alkyl, aryl, or vinylic, and an ether can either be an open chain or a ring. Perhaps the most well known ether is diethyl ether, a familiar substance that has been used medically as an anesthetic, and is used industrially as a solvent.

\begin{center}
\textbf{diethyl ether}
\end{center}
Ethers: Properties

1. Intermediate polarity - usually have dipoles & can accept Hydrogen bonds
2. Not miscible with water - very slight solubility
3. Good solvents for many organic compounds
4. Less dense than water $\rho < 1.0$ - floats on water
5. Usually chemically unreactive - inert to base - can react with very strong acid

Naming Ethers

Two systems for naming ethers are allowed by IUPAC rules. Simple ethers with no functional groups are named by identifying the two organic substituents and adding the word ether as in the below examples.

- Diethyl ether
- Dimethyl ether
- Ethyl methyl ether
- Ethyl ether
- Methyl ether

If other functional groups are present, the ether part is considered to be an alkoxy substituent.

For example, the parent name for the below structure is an alcohol.

- Cockroach sex pheromone
  - 2-methoxy-4-ethylphenol
  - 4-ethyl-2-methoxyphenol
Example:

![THC molecule diagram](image)

Tetrahydrocannabinol (THC)

You should be able to identify different functional groups in a big molecule like THC, and be able to find stereogenic centers and identify the configurations. If treated with Br₂, which double bond will react? *Answer:* Top one (The non-aromatic alkene).

**Stereochemistry Review**

Stereochemistry is refers to the three dimensional arrangement of atoms in space. Stereoisomers are different compounds (different physical properties) that have the same connectivity but a different 3D arrangement of atoms.

Conformers are different shapes of the same compound obtained by rotation around single bonds - usually rapid at room temp 15-20 kcal/mole available at room temp.

Resonance Forms are different pictures of the same compound obtained by movement of electrons, while keeping atom positions same.

A **chiral** molecule (or object) is one that has a non-superposable mirror image.

An **achiral** molecule has mirror images that are superimposable.

A superimposable mirror image for an arbitrary molecule is shown below:

![Mirror image comparison](image)

Image 1 and image 2 are mirror images of each other. The “imaginary” mirror is denoted by the dotted line. Comparison of the two images may not be obvious. So what we have
done is rotate the C-H bond of image 2 for 180 degrees to put all the atoms in the same position as in image 1. We see that after the rotation, image 1 and image 2 are superimposable (superposable) with each other. Therefore, the arbitrary molecule is achiral.

There is also a place of symmetry in the molecule:

This molecule has a plane of symmetry shown by the dotted line. We can see that the left side of the molecule is identical to the right side (these are the X groups and they are symmetric).

A chiral molecule has a non-superimposable mirror image and does not have plane of symmetry. A simple example of a chiral object would be your hand. Your left hand is not superimposable onto your right hand. They are not identical.

A non-superimposable mirror image for an arbitrary molecule is shown below:

In this example, substituent X is not equivalent to substituent Y.

We have done the same thing for achiral molecule. Take the molecule, draw the mirror image of it. However, in this case, when we rotate image 2 of the molecule, we see that it is not the same as image 1. Although the H and CH$_3$ groups are in the same position, the X and Y substituents cannot be put to the same place. In image 1, X is pointed outward, whereas in image 2, X is pointed inward. The two mirror images are not superimposable with each other. Therefore, the molecule is chiral. There is also no plane of symmetry as X group is not the same as Y group.

Tetrahedral atoms (i.e. carbon) with 4 different groups attached are called a **stereogenic centers**. A chiral molecule usually (not always) has a stereogenic center.
Stereoisomers that are non-superposable mirror image of each other are **enantiomers**. All other stereoisomers (which are not mirror images) are called **diastereomers** or **diastereoisomers**.

Example:

Molecules are 3 dimensional objects - we depict in 2 dimensions

![Camphor Structures](image)

Camphor structures - same or different? 

different: they are enantiomers

Compare:

![Structural Isomers and Conformers](image)

Example:

![Butene Isomers](image)

*cis*-2-butene  *trans*-2-butene

These *trans* and *cis* isomers are diasteromers. They are not mirror images.
To compare the relationship of 2 structures:

1. Do they have the same molecular formula? If No, Not isomers.
   If Yes, proceed.

2. Do they have the same sequence of atoms (ie connectivity)? If No, Constitutional or Structural isomers.
   If Yes, proceed.

3. Are they superimposable? If Yes, Identical.
   If No, proceed.

4. Are they mirror images of each other? If Yes, Enantiomers (Non-Superimposable mirror images).
   If No, Diastereomers.

Examples:

- Identical
  - Achiral (not chiral)
  - No stereogenic centres
  - Plane of symmetry

- Identical
  - Achiral (not chiral)
  - No stereogenic centres
  - Plane of symmetry
A is achiral, there is a plane of symmetry going down the middle of the molecule. It does have stereogenic centres, but overall is achiral and it is a **meso** compound. B and C are chiral.

A and B are diastereomers, as are A and C. (A does not have an enantiomer as it and its own mirror image are superimposable = identical).

B and C are enantiomers of each other.

**R/S Nomenclature of Stereogenic Centers - Review**

To assign the configuration of a stereogenic center, a set of rules, the Cahn-Ingold-Prelog rules, were created. The configuration at a stereocenter is described as being R, from Latin *rectus* (or right-handed), or S, from the Latin *sinister* (or left-handed), depending on the order in which the different substituents are arranged around the stereocenter. The rules that are applied are as follows:

1) Each group attached to the stereocenter is assigned a priority, where the higher the atomic number, the higher the priority. For example, Cl > O > N > C > H. For isotopes of the same atom, the one with the higher atomic weight takes priority. Tritium, an isotope of hydrogen, has an atomic weight of 3 and has a higher priority than deuterium which has an atomic weight of 2. Hydrogen with an atomic weight of 1 has the lowest priority. T > D > H

2) If two identical atoms are attached to the stereocenter, the next atom in both chains are examined until a difference is found moving away from the stereocenter. A priority assignment is made at the first point at which the atoms of different priorities are found.
3) A double bond is counted as two single bonds for both atoms involved.

\[ \text{C} = \text{C} \quad \text{equiv.} \quad \text{C} - \text{C} \quad \text{C} = \text{O} \quad \text{equiv.} \quad \text{C} - \text{O} \]

The same principle is extended to triple bonds.

\[ \text{C} = \text{C} \quad \text{equiv.} \quad \text{C} - \text{C} \quad \text{C} = \text{N} \quad \text{equiv.} \quad \text{N} - \text{C} \]

4) After priorities have been assigned, the molecule is viewed with the lowest priority away from the viewer. If you can trace a clockwise path from the group of highest priority to the one of second priority and then to the one of third priority, the stereocenter is assigned the R configuration. If the arrangement is in a counterclockwise path, the stereocenter is assigned the S configuration.

Examples:

![Steroid skeleton](image)

**Cholesterol** is a steroid

Carbon centre bearing alcohol is S

The enantiomer of cholesterol

It has 8 stereogenic centres, which means that it has \(2^8 = 256\) stereoisomers, 1 is cholesterol, 1 is the enantiomer, and the other 254 are diastereomers.
Example: R-3-methoxy-4-methyl-1-pentyne

Quinine is an anti-malarial compound from the *Cinchona officinalis*. It has five stereogenic centres and a wide range of different functional groups including an ether, alcohol, amines (2), aromatic rings (2), alkene.

The priority decreases clockwise but the smallest group is pointing towards you. Therefore, the centre is the opposite (i.e., it is S instead of R)

The R/S configuration of the alcohol is shown to be R. The highest priority is given to the oxygen and the lowest given to the hydrogen. The carbon “next door” to the stereogenic center that is bonded to the nitrogen takes higher priority than the carbon in the aromatic ring since nitrogen has a higher atomic number than carbon. When the hydrogen is pointing away, a clockwise path is found and is assigned the R configuration.

Since there are 5 stereogenic centres, there are $2^5 = 32$ stereoisomers, 1 is quinine, 1 is the enantiomer, and the other 30 are diastereomers