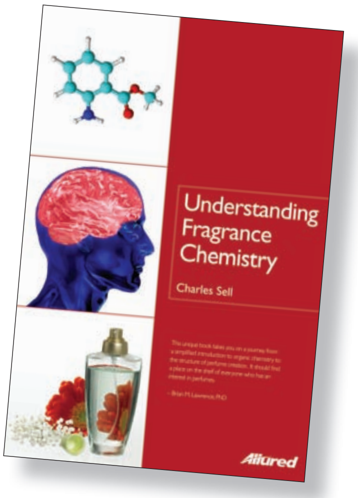
Understanding Fragrance Chemistry

In an excerpt from his new book, Charles Sell delves into the forces driving organic chemical reactions in fragrances

Charles Sell



Fragrance ingredients are organic chemicals (i.e., chemicals with structures based on carbon) and so their chemistry is part of organic chemistry. Chemical reactions basically occur when instability or imbalance exists in atoms, molecules or ions. Stable, neutral atoms such as helium, or molecules such as nitrogen (N_2), require considerable persuasion to undergo chemical reactions. Organic reactions can be classified into four groups: cationic, anionic, free radical and pericyclic. **F-1** shows three ways of removing a hydrogen atom from an organic molecule, methane in this case, in order to produce an unstable, and hence reactive, species.

On the left-hand side of **F-1**, only the hydrogen nucleus has been removed. Therefore, the resulting carbon atom has an orbital with two electrons in it but no other atom attached. A quick count of protons and electrons will reveal that it now has one more electron than protons, so the species is an anion carrying one negative charge. Such species are known as carbanions. In the center, the hydrogen nucleus has been removed together with one electron leaving a carbon species that is neutral but contains an unpaired electron. Such a species is known as a free radical. On the right, the hydrogen nucleus and both electrons of the carbon-hydrogen bond have been removed, thus leaving a positively charged species known as a carbocation. These three species are all unstable and hence reactive.

The carbanion and carbocation shown in **F-1** are very unstable and are rarely seen in real chemistry. The carbanions and carbocations that we come across in fragrance chemistry are usually stabilized in some way relative to their methyl counterparts, but they are still reactive.[*]

Chemical reactions involve transfer of electrons from one entity to another, which are represented in figures by curled arrows. A normal double-headed arrow is used when two electrons are involved and a single-headed arrow when only one electron is involved. Using this convention, we can rewrite the reactions of **F-1** as shown in **F-2**, now also including the reagents used to carry out the abstraction of the various hydrogen species.

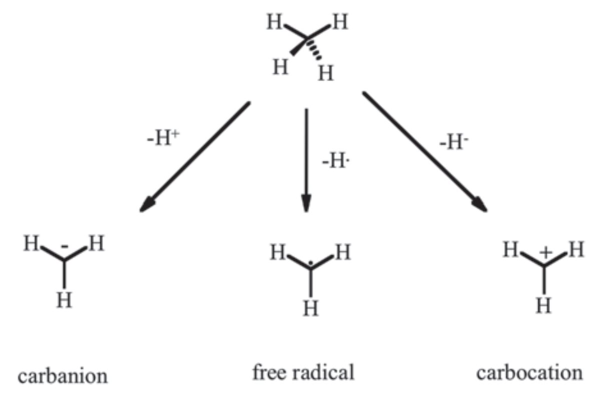
On the left of **F-2**, the electron pair of an anion has formed a bond between the anion and one of the hydrogen atoms of the methane molecule. The electron pair that formed the bond between that hydrogen atom and the carbon are then displaced onto the carbon atom to form a methyl carbanion. In the center of the figure, one electron from a radical and one from the C-H bond joined together to form a new bond between R and the hydrogen

---

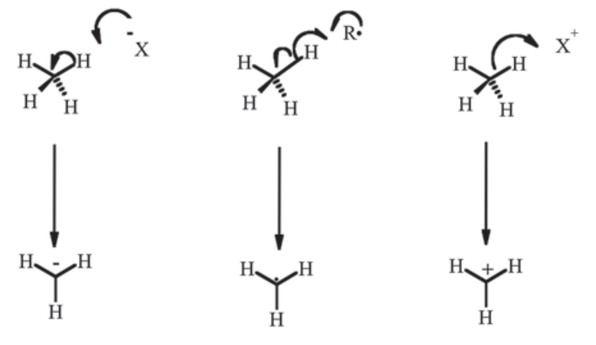
[*] This topic is discussed further in other chapters of Sell's forthcoming book, *Understanding Fragrance Chemistry.*

Understanding Fragrance Chemistry* by Charles Sell is coming soon! For more information, please visit *www.perfumerflavorist.com/bookshelf.

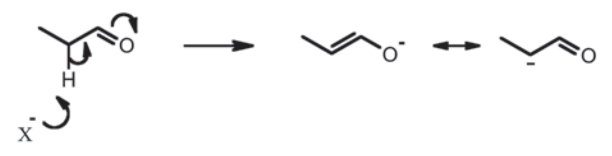
Formation of ions and radicals from methane **F-1**



Mechanistic illustration of formation of ions and radicals from methane **F-2**



Formation of an enolate anion **F-3**



atom. The other electron of the C-H bond moved onto the carbon atom to form a methyl free radical. On the right of the figure, a cation removed the hydrogen atom and the pair of electrons that bonded it to the carbon atom to leave the methyl carbocation.

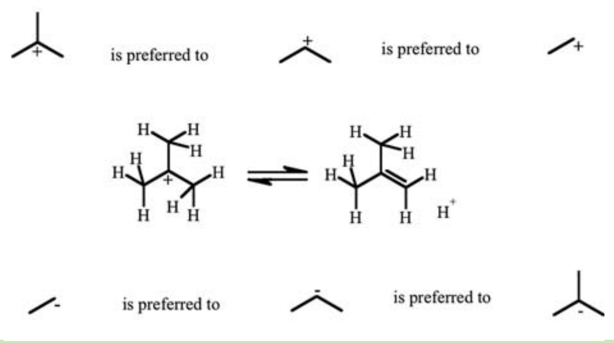
In a previous chapter (chapter 3), it was described how carbon-oxygen bonds are polarized with a partial negative charge over the oxygen atom and a corresponding partial positive charge over the carbon atom. This polarization applies to carbon oxygen double bonds also, and, consequently, all aldehydes, ketones and esters have a partial positive charge on the carbonyl carbon. (The adjective carbonyl refers to any carbon-oxygen double bond.) The inductive effect occurs when the effects of charges are felt through bonds. Therefore, the positive charge on a carbonyl carbon is felt not just on that carbon atom but also on adjacent carbon atoms and on the hydrogen atoms attached to them. Thus, as shown in **F-3**, the hydrogen on the carbon α (i.e., immediately adjacent) to an aldehyde group is positive enough to be able to be removed by an anion, and the electrons are pulled onto the oxygen atom of the aldehyde. The resulting species is known as an enolate anion since it could also be considered to have been formed by removal of a proton from the enol form of the aldehyde. The oxygen atom and the α-carbon share the negative charge on the enolate anion and so, reactions can occur at either of these atoms. This resonance between the two canonical forms also provides stabilization for the anion. In practice, this process is the most important way in which carbanions are formed.

If a carbon-hydrogen bond is considered to be completely polarized, then the result is a positive charge on the hydrogen atom and a negative charge on the carbon. Based on this concept—which is called hyperconjugation—alkyl residues tend to donate electrons to their neighbors. Therefore a primary carbanion is more favored than a secondary. A secondary is, in turn, more favored than a tertiary, and so on. As the number of alkyl groups increases so does the addition of more negative charge from hyperconjugation. It is obviously not favorable to push more electronegativity onto a negative charge. Conversely, carbocations are stabilized by having more alkyl groups around them. This example is illustrated in **F-4**. In the center of the figure, two canonical forms of a tertiary-butyl carbocation are shown to demonstrate how hyperconjugation stabilizes the positive charge.

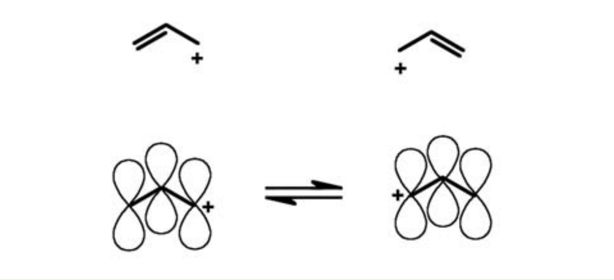
Charges, particularly positive charges, are also stabilized by conjugation with double bonds and aromatic rings. **F-5** shows such stabilization in action using both line drawings of bonds and also a representation of the orbitals involved.

From the point of view of fragrance chemistry, the two most important ways of forming carbocations are by addition of a proton to a double bond or by elimination of water from a protonated alcohol. Both of these processes are shown in **F-6**. In the upper part of the figure, the electron pair of the π-bond forms a new bond with the incoming proton, which leaves one of the carbon atoms of the starting olefin as a carbocation. In the lower case, a lone pair of electrons on the oxygen atom forms a bond to the proton, leaving the oxygen atom carrying a positive charge. The electrons of the carbon-oxygen bond of the alcohol then leave and move onto the oxygen to form a new lone pair, thus leaving the positive charge on the carbon atom.

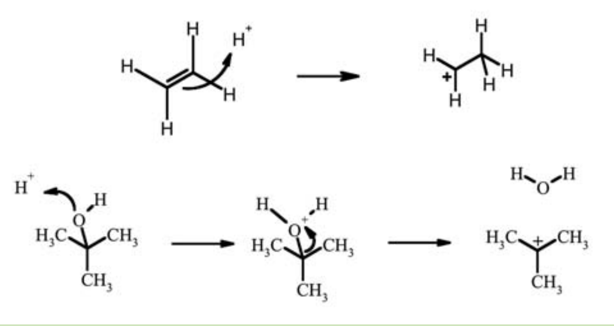
Stabilization of anions by hyperconjugation **F-4**



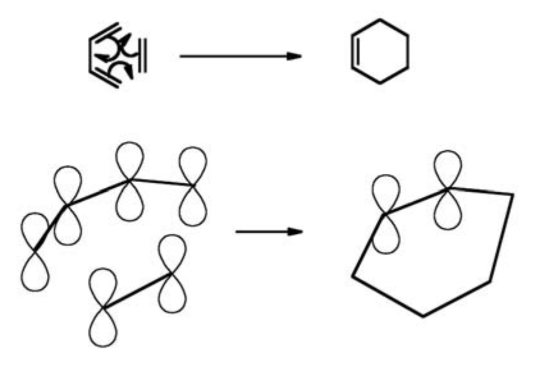
Stabilization of a carbocation by conjugation **F-5**



Formation of carbocations **F-6**



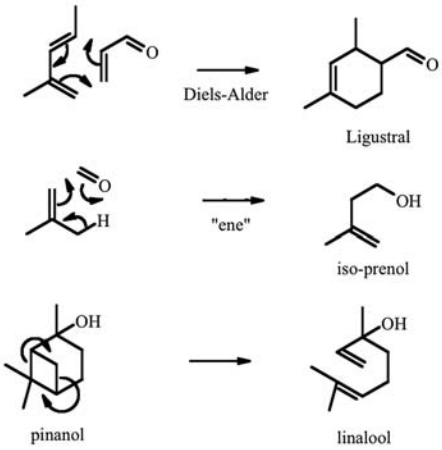
The Diels-Alder reaction **F-7**



Pericyclic (or electrocyclic) reactions involve p-orbitals moving in a ring to form new bond systems. These reactions are essentially synchronous in nature. An example is the Diels-Alder[a] reaction in which a butadiene reacts with an ethylene to form a cyclohexene, as shown in **F-7**, again using both line drawings of bonds and also a representation of the orbitals involved.

The Diels-Alder reaction is classified as a 4+2 reaction since one of the components, the diene, has four atoms that take part in the reaction, while the other, the dienophile, has two. An example of a Diels-Alder reaction of use in perfumery is shown in **F-8**. The top scheme in the figure shows the reaction of methylpentadiene with acrolein (propenal) to form Ligustral, which provides green topnotes in fragrances. Another useful 4+2 reaction is the "ene" reaction shown here being used to form iso-prenol from isobutylene (2-methylpropene) and formaldehyde. In the Diels-Alder reaction, all of the bonds involved in the reacting species are double bonds but the "ene" reaction is different in that one of the reacting bonds is a C-H single bond. Iso-prenol is an important feedstock for the preparation of terpenoid compounds.[*] The third reaction shown in **F-8** is a 2+2 reaction since only four electrons are involved. The formation of a cyclobutane from two ethylene molecules is an analogy of the Diels-Alder reaction; it builds a ring from acyclic precursors. This reaction is the reverse. In other words, a ring is broken with the formation of two double bonds. This reaction is the thermal cracking, or pyrolysis, of pinanol to give linalool and it requires high temperatures. It is an important route to linalool and other terpenoid fragrance ingredients.[*]

Some pericyclic reactions used to prepare fragrance ingredients **F-8**



---

[a] Many organic chemistry reactions are named after the chemists who discovered them. In this case, the reaction was discovered by two chemists working together, Otto Diels and Kurt Alder.

[*] This topic is discussed further in other chapters of Sell's forthcoming book, *Understanding Fragrance Chemistry*.

To purchase a copy of this article or others, visit www.PerfumerFlavorist.com/articles. p&f