The Chemistry of Lipids

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The term ‘lipids’ describes a hotchpotch of heterogeneous structures; yet they all have two things in common: they are fatty, and high in energy. Lipids do not dissolve in water, or only do so partially - which means they are lipophilic or hydrophobic (they do, however, dissolve well in solvents) - and they are all made from energy-rich units of activated ethanoic acid, so-called acetyl-CoA units. These two properties, plus the way lipids appear in many different forms, means they are destined for a variety of important functions within the human body. In addition to other things, they constitute building materials, message-carriers, and combustible materials. You can read about the properties, structure, and functions of lipids below.

Properties of Lipids

Lipids are either completely lipophilic and therefore completely apolar, or predominantly apolar. A lipid (or the lipid component of a compound) will dissolve in water either poorly or not at all but will dissolve in solvents such as alcohol and ether.

Grease drops sitting on top of chicken bouillon is a good example of the non-solubility of fats in water. When fat is being digested (for example after eating the chicken bouillon in question), mixed micelles spontaneously form within the digestive tract, with the help of bile acid. Micelles are spherical aggregates. They are amphiphilic, meaning they are lipophilic inside, and hydrophilic molecular components are found on the outside. During the spontaneous formation of micelles, all lipophilic components within the environment are included in these spherical aggregates. After that, the micelles migrate through the digestive tract for some time, and then passively enter the mucosal cell where they are further transformed and transported to their destination.

Outside the body, lipids can bond with the help of detergents. These water-soluble organic substances reduce the surface tension, which binds the fat. Detergents can be
found for example in dish soap.

The Classification of Lipids

Lipids are a very heterogeneous group and can be classified differently, depending on the parameters considered.

**Structural classification**

The rough structural classification of lipids is based on the **distinguishing of fatty acids (and their derivatives) from polyprenol compounds**.

Fatty acids are placed into different categories, depending on which component they combine with. These different precursors are all combined with one or more fatty acids. These fatty acids include, for example, **triglycerides**, which constitute the structural fat within the human body, and **sphingolipids**, which are involved in the development of the nervous system.

**Polyprenol compounds**, on the other hand, do not contain fatty acids. Instead, they arise from the **precursor, isoprene**. Via folding and extension, they form useful substances such as fat-soluble vitamins, **steroids** (e.g., cholesterol), and terpenes, which we are familiar with in the form of the menthol in cough sweets.

![General Chemical Structure of Sphingolipids](image)

**Functional classification**

Another way of classifying lipids is based on their function. It is possible to divide lipids according to the nature of their fatty acids and their chemical backbones. The main backbones are:

- Glycerol
- Sphingosine
- Isoprene

**Glycerol** backbone lipids are part of the key component of the cell lipid bilayer. Additionally, they serve as key parts of intracellular and extracellular proteins, as well as, some second messengers.

**Sphingosine** based lipids are involved in the cell layer as well, but instead of being part of the signaling pathways, they are more readily recognized as being part of the cell to
cell recognition pathways. Also, there are many sphingosine based lipids, such as ceramide, involved with apoptosis, autophagy, cell differentiation, and other processes.

Interestingly, the isoprene based lipids form the base of many vitamins, including vitamins A, E, and K.

### Classification according to the reaction with water

Another variation in the classification of lipids is based on their reactivity with water. This reaction is called **hydrolysis** and the hydrolysis of fats is specifically referred to as **alkaline hydrolysis**. However, this is not possible with every kind of fat, thus **non-hydrolyzable** lipids include hydrocarbons (β-carotene), alcohols (cortisol), and acids (linoleic acid). However, those that are **hydrolyzable** include certain (simple) esters (triglycerides in dietary fat, cholesterol), phospholipids (phosphatidylcholine), sphingolipids (e.g., membrane lipids of the nervous systems), and glycolipids (neural membrane lipids).

### Fatty Acids

When dealing with the chemistry of lipids, fatty acids require extra review since all lipids have, as mentioned above, a common structural element: activated acetic acid, i.e. acetyl-CoA. **Acetyl-CoA is the central substance in lipid metabolism.**
Fatty acids are **carbon chains of various lengths**, with at least 4 carbon atoms. Up to 4 hydrogen atoms can be bound to the carbon atoms. At one end of the carbon, the chain is a **methyl group**, i.e., a carbon atom with 3 hydrogen atoms (CH₃); and, at the other end is an acidic **carboxyl group (COOH)**, which is why the carbon chain is also called an acid.

Fatty acids are **amphiphilic** because they have both a lipophilic end (carbon part) and a hydrophilic end (carboxyl group). The longer the carbon chain, the more the fatty acid acts in a lipophilic manner since the carbon part is responsible for the lipophilic properties. The opposite is true for short carbon chains, in which hydrophilic properties dominate, due to the influence of the hydrophilic carboxyl group.
Fatty acids can be found either separately or attached to other compounds. Fatty acids can be saturated or unsaturated. The most important building blocks for the human organism with respect to esterification (i.e., the combining of fatty acids with another molecule) are glycerol (tertiary alcohol), isoprene (unsaturated hydrocarbon), and sphingosine (unsaturated amino alcohol).

The nomenclature of fatty acids

Fatty acids can be named in several ways. Firstly, they can be named depending on the number of double bonds. If there is no double bond, then we are dealing with a saturated fatty acid; this means that there are 4 hydrogen atoms bound to each carbon atom, hence, all binding sites are occupied (saturated) and the carbon atoms are bound by single bonds.

A monounsaturated fatty acid has 1 double bond between 2 carbon atoms at any point in the carbon chain, as not all binding sites are occupied by hydrogen atoms (unsaturated). Polyunsaturated fatty acids have at least 2 or more double bonds in the carbon tail.

The configuration of the double bond may also be denoted as cis-$\Delta^9$-oleic acid. The ‘cis’ means that the spatial arrangement of the double bond can be conceived as a trapezoid. A trans configuration means that the double bond lies on the opposite side. All unsaturated fatty acids in the human body have a cis configuration.

Various trans-fats are well-known in the food industry. These fatty acids are characterized by the fact that their double bond is configured differently, compared to the ‘normal’ cis fatty acid. Such trans-fatty acids are produced via the technological hardening of vegetable fat—for example in the manufacture of margarine. Trans-fatty acids have been discredited as promoting arteriosclerotic vascular alterations. Statutory regulations have now been established in many countries to reduce the number of trans-fats in food.

Besides counting from the carboxyl end, the position of the double bond can also be
determined by counting the carbon atoms from the other side. In this case, an omega (Ω) is written in front of the position of the double bond. This is the notation used for the well-known omega-3 and omega-6 fatty acids. Important examples of these fatty acids are:

- **Linoleic acid**: Linoleic acid is a **ω-6 fatty acid** (18:2 cis-Δ9,12; meaning 18 carbon atoms and 2 double bonds at positions 9 and 12 from the carboxyl end, or at position 6, counting from the methyl end).
- **Linolenic acid**: Alpha-linolenic acid is a **ω-3 fatty acid** (18:3 cis-Δ9,12,15; meaning 18 carbon atoms and 3 double bonds at positions 9,12, and 15, counting from the carboxyl end, or at position 3 when counting from the methyl end).
- **Arachidonic acid**: Arachidonic acid is also a **ω-6 fatty acid** (20:4 cis-Δ5,8,11,14; meaning 20 carbon atoms and 4 double bonds at position 5,8,11, and 14, counting from the carboxyl end, or at position 6 counting from the methyl end).

Lastly, fatty acids can be specified in terms of whether the double bonds of the polyunsaturated fatty acid are isolated or conjugated. In humans, the double bonds of fatty acids are always isolated, which means that there are at least 2 single bonds between the double bonds. Conjugated double bonds are present if single and double bonds alternate with each other.

**The significance of fatty acids**

Fatty acids have multiple functions and are essential to the structure and function of the human body. They occur either by themselves, i.e. in isolated form—for example as **transmitters** such as eicosanoids (which are synthesized from arachidonic acid)—or in combination with other substances—for example, together with glycerol as **storage fat** (triglycerides).

One way of getting fatty acids into the body is through food. Saturated fatty acids are mainly found in animal products, whereas plants often incorporate double bonds into their fatty acids, which means the human intake of unsaturated fatty acids is mainly via vegetable fats. The particularly valuable polyunsaturated fatty acids, which are commonly found in fish oil, are an exception. **Essential fatty acids** are found in vegetable oils, such as linseed oil, and in fish oil, for example.

**Long-chain fatty acids** are crucial to the human body. Most fatty acids that are commonly eaten are relatively long. That means that they consist of at least 16 carbon atoms (e.g., palmitic acid). The human body can produce fatty acids from carbohydrates on its own, and can even insert double bonds, but this is only possible beyond carbon 9. However, since double bonds beyond carbon 9 are needed for specific functions, 3 specific fatty acids have to be supplied from an external source, namely the **essential fatty acids** linoleic acid and linolenic acid, and the semi-essential arachidonic acid.
In impaired fat digestion, short- and medium-chain fats are used in the diet. These fatty acids consist of only 4–12 carbon atoms and can be absorbed directly into the bloodstream without any input from pancreatic lipase. These so-called MCT (medium-chain triglyceride) fats are an important dietary supplement for patients with conditions like short bowel syndrome.

An important function of fatty acids is related to 'local' hormones, the eicosanoids. These are produced from arachidonic acid. They are either supplied via food or produced from the essential linoleic or linolenic acid via elongation (elongation of the carbon chain) and desaturation (integration of a double bond).

Arachidonic acid (C:20:4, Ω-6 fatty acid) is produced from linoleic acid (C:18:2, Ω-6 fatty acid); and eicosapentaenoic acid (C:20:5, Ω-3 fatty acid) or docosahexaenoic acid (C:22:6, Ω-3 fatty acid) is formed from linolenic acid (C:18:3, Ω-3 fatty acid). These polyunsaturated fatty acids improve membrane fluidity. The eicosanoids prostaglandin, thromboxane, and leukotriene are formed from arachidonic acid (eicosatetraenoic acid). These substances are lipid mediators and act directly within the tissue in which they are released (hence the name ‘local’ hormones). They are involved in inflammatory responses, hemostasis, and the vasodilation of vascular capillaries, for example, along with numerous other processes. They are described in detail in the corresponding chapter.

A lack of essential fatty acids can have severe consequences as it may result in a breakdown in membrane structure, leading to a breakdown in intracellular metabolism. A lack of essential fatty acids may be evidenced by non-specific symptoms such as skin eczema and increased susceptibility to infection, or visual disturbances.

Storage Lipids

The properties of storage lipids

Fat is an excellent energy source (1 g provides 9 kcal of energy or 39 kJ per mol), and fat can be stored very efficiently in terms of space as water is not essential to its storage (glycerol in the muscle also supplies energy but, since it is hydrophilic and is stored with water, this method of storing energy takes up very limited space). These properties mean that lipids are well-suited as an energy store for times of need, and this storage can be expanded almost indefinitely.

Esterification: how fat becomes a storage

Triglycerides are commonly referred to as storage fat. Triglycerides, also called triacylglycerides or triacylglycerols, are categorized as glycolipids, as the tertiary alcohol glycerol is esterified with 3 fatty acids. A triglyceride is, therefore, a fatty acid ester. Various fatty acids can be esterified with glycerol.

Palmitic acid (C:16:0) and stearic acid (C: 18:0) are usually found within storage fat. You
may sometimes come across the term ‘neutral fat’. The term ‘neutral fat’ also includes triglycerides as these molecules are uncharged, i.e. neutral. Triglycerides do not only serve the purpose of food storage—but can also be found in subcutaneous fat due to their strong insulating properties, and as structural fat owing to their protective properties. Examples of these may be seen in the orbital cavity (the eye socket) or in the renal capsule.

**Cholesterol esters**

By means of esterification, hydrophilic groups can be packaged in such a way that allows them to be converted from being polar to neutral. This is how cholesterol is made transferable and storable. The cholesterol molecule is actually a very lipophilic molecule, which is why it can easily be stored as lipid droplets; however, it also possesses a hydroxyl group (OH group). This OH group is hydrophilic, meaning the above-mentioned form of storage is not possible. Esterification is the only method that facilitates the storage of cholesterol as cholesterol ester within the cell interior (cytosol) as it involves the cholesterol molecule being made nonpolar (neutral). The enzyme acyl-CoA-cholesterol acyltransferase performs this esterification within the cell interior.

Esterification also aids the transportation of this special molecule through the bloodstream. The amphiphilic structure of this molecule (which includes both a large lipophilic part and a small hydrophilic part) specifically prevents micelle formation. This intermediate esterification, performed for the purpose of transport, is what allows cholesterol to be transported with the aid of lipoproteins (such as LDL). The esterification is performed by specific acyltransferases, which—as their name suggests—transfer an acyl group. The acyl group is a fatty acid, such as oleic acid or stearic acid. The acyltransferase present in the bloodstream and responsible for this task is lecithin-cholesterol acyltransferase (LCAT). This enzyme uses lecithin for the esterification of a fatty acid.

Cholesterol has very diverse functions within the human body. It is an important membrane lipid and a starting substance for steroids. Steroid hormones regulate a variety of physiological functions. Important steroid hormones are the sex hormones, such as estrogen, progesterone and testosterone, and the adrenal hormones aldosterone and cortisol.

**From triglycerol to di(acyl)glycerol to mono(acyl)glycerol**

Glycerol can be esterified with 3 fatty acids, although this does not have to occur. There are also variants that have 2 fatty acids (diacylglycerol, DAG) or only 1 fatty acid (monoacylglycerol). When building a triglycerol, an intermediate is formed—for example, a diglycerol. DAG plays a significant role in transmitting signals to the membranes. In this case, the DAG is formed by a kinase from membrane-bound phosphatidylinositol. Monoacylglycerols are formed during the digestion of lipids by the action of lipases, with the goal of creating short lipophilic units for the formation of micelles.
Membrane Lipids

The properties of membrane lipids

Besides their storage function, one of the main purposes of lipids is found within the membranes of the organism. Every biological membrane consists of lipids. The well-known components are glycerophosphatides, sphingosine phosphatides (which are located in the membranes of the CNS), and cholesterol.

As an intermediate product, lysoglycerosphospholipid is formed. This molecule has a regulatory function as a signaling substance with respect to the neuronal membranes.
All membrane lipids have both hydrophobic and hydrophilic parts; thus, they are **amphiphilic** and this is a basic requirement for constructing a biological membrane. The biological membrane consists of a **lipid bilayer**.

In an aqueous environment, the membrane's hydrophobic lipid tails are spontaneously oriented inwards and the hydrophilic lipid parts are oriented outwards, whereby the lipid bilayer is formed. This layer forms a natural barrier, isolating the compartments and the structures from each other. Proteins embedded into the membrane permit the transfer of a directed exchange of signals and of material, which can be regulated by lipid head group reactions.

The spontaneous bilayer orientation of membrane lipids is employed in drugs, for example. Apolar substances, such as certain drugs, can be transported through polar media in **liposomes**, which are vesicles whose shell is similar to a cell membrane.

### The structure of membrane lipids

#### Glycerophosphatides

As with triglyceride, the tertiary alcohol glycerol forms the backbone for the glycerophosphatides, but there are only 2 fatty acids attached to the 3 possible binding sites, and a phosphate group is bound to the third carbon atom of glycerol.

Yet another molecule is bound to this phosphate group. The bonds that are formed are called **ester bonds**. This is why this is also referred to as a **phosphate diester** bond – as 2 ester bonds result, starting from the phosphatide (dissociated phosphatide acid). In contrast to triglyceride, the glycerophosphatide combines 2 contrasting features: the entire molecule has both a nonpolar part (glycerol with 2 esterified fatty acids) and a polar part (the phosphate group with another polar binding partner).

Various polar groups can be esterified with the phosphatide group on glycerol's 3rd carbon atom. A well-known example is the amino alcohol, choline, which involves the formation of **phosphatidylcholine** (better known as **lecithin**). Other glycerophosphatides are **phosphatidyserine** (serine is an amino acid), **phosphatidylethanolamine** (also known as **cephalin**; ethanolamine is amino alcohol), and **phosphatidylinositol** (inositol is an amino alcohol). Another example of a glycerophosphatide is **diphosphatidylglycerol**, which is also known as cardiolipin and is found exclusively in the mitochondrial membrane.
Sphingosine phosphatides

Sphingosine phosphatides are the main component of membranes that are located within the CNS. In these compounds, it is not glycerine that forms the backbone but sphingosine, to which fatty acids and phosphates are bound. Sphingosine is an amino alcohol that is always present in the body, with a fatty acid attached to it (by an amide bond). This molecule is called ceramide. Numerous derivatives are based on ceramides such as sphingomyelin (a phospholipid) or the glycolipids cerebroside and ganglioside.

Sphingomyelin is located mainly in the myelin sheaths of the neurons. The hydroxyl group of ceramide is esterified with a phosphate group. Additional amino alcohol, choline, is bound to this phosphate group.

The cerebrosides are mainly found in the membranes of nerve cells and the substantia alba (white matter) of the brain; they also exist in the gangliosides in the brain and in the ganglia. Starting from ceramide, a carbohydrate group is bound to the hydroxyl group. If it is a monosaccharide—in most cases, it is galactose—then galactosylceramide is formed, which is also referred to as cerebroside. Sometimes, other things are bound to the hydroxyl group. Three to six complex carbohydrate groups can be connected to each other in gangliosides, one of which is the amino sugar N-acetylneuraminic acid.

Gangliosidosis, a hereditary disease, is the accumulation of gangliosides in the CNS and loss of the affected cells. Severe developmental disorders result. Examples are Tay-
Sachs disease and Niemann-Pick disease.

Cholesterol

Cholesterol has diverse functions in the human body, and as an amphiphilic molecule, it also is present in biological membranes. This characteristic is a result of its nonpolar ring system and its hydrophilic hydroxyl group. Cholesterol supports the construction of the lipid bilayer by embedding its rings between the fatty acids of the membrane lipids and by influencing fluidity. Optimal membrane fluidity is the basic requirement for the maintenance of functioning membrane permeability and signal transmission.

Membrane-related means of communication

Hydrolysis of the membrane lipids results in the formation of second messengers, which are very important for signal transmission:

**Inositol triphosphate (IP$_3$)** and **DAG** are formed from the membrane lipid phosphatidylinositol. **Phosphatidylinositol-4,5-bisphosphate—PIP$_2$ in short** is formed by double phosphorylation. Then, IP$_3$ and DAG can be formed by the hydrolysis of PIP$_2$. Both molecules are involved in signal transduction cascades: DAG activates protein kinase C, and IP$_3$ stimulates the intracellular release of calcium.

**Reactions with Reactive Oxygen Species**

Just as butter becomes rancid when it reacts with oxygen, free oxygen radicals in the membrane lipids can also cause a reaction. Free radicals are formed as a byproduct of many reactions in the organism, such as mitochondrial ATP production in the respiratory chain. If there are esterified (poly)unsaturated fatty acids in the membrane, then lipid peroxidation, a reaction with free radicals, may easily occur. This creates a fatty acid radical which is very reactive and will react with the fatty acids within the environment. This may lead to profound structural changes in the membrane and cause inflammation.

References


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