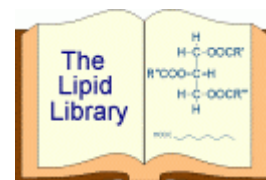# FATTY ACIDS: STRAIGHT-CHAIN SATURATED

STRUCTURES, OCCURRENCE AND BIOSYNTHESIS

Structure, Nomenclature and Occurrence

Straight- or normal-chain, saturated components (even-numbered) make up 10-40% of the total fatty acids in most natural lipids. The most abundant saturated fatty acids in animal and plant tissues are straight-chain compounds with 14, 16 and 18 carbon atoms, but all the possible odd- and even-numbered homologues with 2 to 36 carbon atoms have been found in nature in esterified form. They are named systematically from the saturated hydrocarbon with the same number of carbon atoms, the final 'e' being changed to 'oic'. Thus, the fatty acid with 16 carbon atoms and the structural formula -

$CH_3(CH_2)_{14}COOH$

COOH

hexadecanoic (palmitic) acid
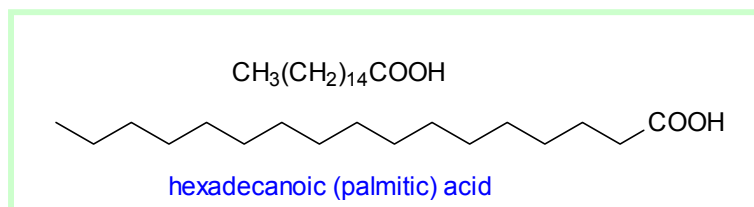
- is systematically named **hexadecanoic acid**, although it is more usual to see the trivial name palmitic acid in the literature. It can be termed a 'C_{16}' fatty acid or with greater precision - '16:0', the number before the colon specifying the number of carbon atoms, and that after the colon, the number of double bonds. A list of saturated fatty acids together with their trivial names and shorthand designations is given in the table below. Trivial names are best avoided, and I have not listed the more obscure of these (a comprehensive list is available on the AOCS web site (see our **Links** page). However, this advice is perhaps too pedantic for the most common of these fatty acids.

Long-chain saturated fatty acids (12:0 upwards) have relatively high melting points. Animal fats and seed oils such as palm oil in which these components are especially abundant tend to be solids at room temperature. Such saturated fatty acids also increase the rigidity of membranes.

Not everyone would consider **formic acid** to be a fatty acid, but it has been identified in esterified form in phosphatidylcholine from human neutrophils, with 16:0, 18:0 or 18:1 as the other fatty acid.

Acetic or ethanoic acid (2:0) is of great importance in living tissues, as the biosynthetic precursor of fatty acids and innumerable other metabolites. However, it is not often found in association with fatty acids of higher molecular weight in esterified form in lipid molecules, although it does occur esterified to glycerol in ruminant milk fats (presumably in position *sn*-3). It is also the most common fatty acid linked to **platelet-activating factor**. In seed oils, acetic acid

$CH_3C \diagup O \diagdown OH$

acetic acid

occurs in position *sn*-3 of triacylglycerols of *Euonymus verrucosus*, and related species, while in *Polygala virgata* it is in position *sn*-2. In other vegetable oils, it has been detected in linkage to the hydroxyl group of a hydroxy fatty acid, which is in turn esterified to glycerol, i.e. as an estolide. Acetates of long-chain alcohols are found in plant and insect waxes and as insect pheromones. A novel sphingomyelin, isolated from a cyanobacterium, *Scytonema julianum*, contains acetate in an
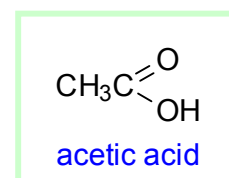
estolide linkage, i.e. with the acetyl group esterified to an ω-1 hydroxyl group in a long-chain fatty acid. An acetylated cerebroside derivative has been found in rat brain myelin, i.e. with an acetyl group linked at the C3 hydroxyl of the sphingosine base. Indeed, acetate is a common constituent of complex sphingolipids, usually in amide linkage to glucosamine, galactosamine, neuraminic acid or even sphingosine.

Systematic name	Trivial name	Shorthand designation
ethanoic	acetic	2:0
propanoic	propionic	3:0
butanoic	butyric	4:0
pentanoic		5:0
hexanoic	caproic	6:0
heptanoic		7:0
octanoic	caprylic	8:0
nonanoic		9:0
decanoic	capric	10:0
undecanoic		11:0
dodecanoic	lauric	12:0
tridecanoic		13:0
tetradecanoic	myristic	14:0
pentadecanoic		15:0
hexadecanoic	palmitic	16:0
heptadecanoic	margaric	17:0
octadecanoic	stearic	18:0
nonadecanoic		19:0
eicosanoic	arachidic	20:0
heneicosanoic		21:0
docosanoic	behenic	22:0
tricosanoic		23:0
tetracosanoic	lignoceric	24:0
pentacosanoic		25:0
hexacosanoic		26:0
heptacosanoic		27:0
octacosanoic		28:0
nonacosanoic		29:0
triacontanoic		30:0
hentriacontanoic		31:0
dotriacontanoic		32:0

Propanoic acid (3:0) is important as the biosynthetic precursor of some amino acids. It is rarely found in esterified form in natural lipids, and to my knowledge the only exception is for molecules related to platelet-activating factor.

Butanoic acid (4:0) comprises 3-4% by weight (much more in molar terms) of the total fatty acids in cow's milk, where it is found exclusively in position 3 of the triacyl-*sn*-glycerols. It is found in milk fats of other ruminants, but not in the lipids of other tissues of these species.

Odd-chain fatty acids from **5:0 to 11:0** have been detected at trace levels in the triacylglycerols of ruminant milks, but not elsewhere in conventional esterified form, as far as I am aware. They are found as oxidation products of long-chain fatty acids, together with a range of even-numbered components (2:0 to 12:0) as urinary acylcarnitines.

Hexanoic acid (6:0) comprises 1-2% of the total fatty acids in ruminant milk triacylglycerols, where most of it is esterified to position 3 of the triacyl-*sn*-glycerols. It is also found as a minor component of certain seed oils rich in medium-chain saturated fatty acids (see below).

Medium-chain fatty acids, such as **octanoic** (8:0), **decanoic** (10:0) and **dodecanoic** (12:0), are found in esterified form in most milk fats, including those of non-ruminants, though usually as minor components, but not elsewhere in animal tissues in significant amounts. They are never detected in membrane lipids, for example. They are absent from most vegetable fats, but with important exceptions. Thus, they are major components of such seed oils and coconut oil, palm kernel oil and *Cuphea* species.

Odd-chain fatty acids from **13:0 to 19:0** are found in esterified form in the lipids of many bacterial species, and they can usually be detected at trace levels in most animal tissues, presumably having been taken up as part of the food chain. In particular, they occur in appreciable amounts (5% or more) in the tissues of ruminant animals.

Myristic acid (14:0) is a ubiquitous component of lipids in most living organisms, but usually at levels of 1-2% only. However, it is more abundant in cow's milk fat, some fish oils and in those seed oils enriched in medium-chain fatty acids (e.g. coconut and palm kernel). This fatty acid is found very specifically in certain **proteolipids**, where it is linked via an amide bond to an *N*-terminal glycine residue.

Palmitic acid (16:0) is usually considered the most abundant saturated fatty acid in nature, and it is found in appreciable amounts in the lipids of animals, plants and lower organisms. It comprises 20-30% of the lipids in most animal tissues, and it is present in amounts that vary from 10 to 40% in seed oils. Among commercial sources, it is most abundant in palm oil (40% or more).

Stearic acid (18:0) is the second most abundant saturated fatty acid in nature, and again it is found in the lipids of most living organisms. In lipids of some commercial importance, it occurs in the highest concentrations in ruminant fats (milk fat and tallow) or in vegetable oils such as cocoa butter, and of course in industrially hydrogenated fats. It can comprise 80% of the total fatty acids in **gangliosides**. Relatively high proportions of stearic acid are metabolized, by desaturation to oleic acid, in comparison to other saturated fatty acids.

Eicosanoic acid (20:0) can be detected at low levels in most lipids of animals, and not infrequently in plants and microorganisms.

Very-long-chain saturated fatty acids (**21:0 to 32:0**) are not usually considered to be common constituents of lipids. However, they do occur in many plant **waxes**, which by some estimates are the most abundant lipids on earth, and in some animal waxes such as wool wax. Saturated fatty acids up to 26:0 are normal constituents of animal and plant sphingolipids.

Biosynthesis of Saturated Fatty Acids

The biosynthesis of saturated fatty acids requires a primer molecule, usually acetic acid in the form of its **Coenzyme A** ester, and a chain extender, malonyl-CoA. The latter is formed from acetyl CoA by the activity of the enzyme acetyl-CoA carboxylase in which biotin is the prosthetic group (and thus can be inhibited by avidin). In the first step of the reaction, carbon dioxide is linked to the biotin moiety, and this is subsequently transferred to acetyl-CoA to form malonyl-CoA. In microorganisms such as *Escherichia coli*, the enzyme complex comprises three dissociable proteins, but in plants and animals, the enzyme is a single multifunctional complex that exists in two main isoforms. Malonyl-CoA is also involved in the regulation of fatty acid oxidation by inhibiting carnitine palmitoyl-CoA transferase-1.
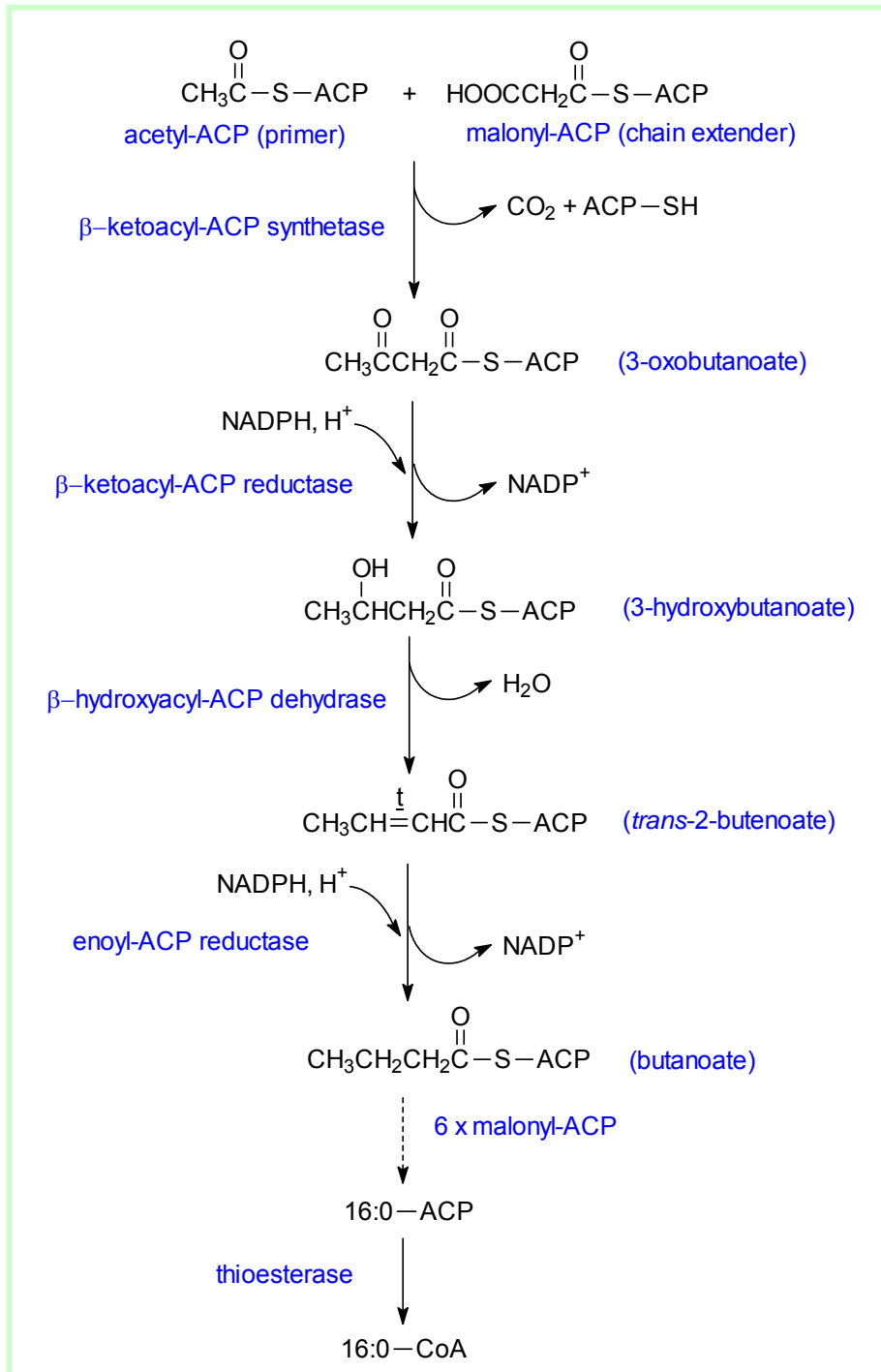
Successive molecules of malonyl-CoA are added to the single primer molecule of acetyl-CoA in a sequence of reactions catalysed by a multifunctional enzyme complex, the fatty acid synthetase, which can be of three types. In the Type I enzyme (FAS I) found in animals, the various sub-units carrying out each step of the reaction are discrete domains of a single protein that is the product of one gene. In yeast and fungi, there are two genes that produce polypeptide products, which then coalesce to form a multifunctional Type I fatty acid synthase complex. Type II enzymes (FAS II) consist of separate proteins encoded by different genes that each catalyse a separate step and can be dissociated and purified, although they normally operate in concert; they are found in bacteria (e.g. *E. coli* - considered the model system), parasites and plants. Type III fatty acid synthetases are also termed 'elongases' and catalyse the addition of C_2 units to preformed fatty acids.

As a first step, both the primer and extender substrates are attached to acyl carrier protein (ACP), which has the same prosthetic group as Coenzyme A. A sequence of reactions follows in which the chain is extended and butanoate is formed, as illustrated. First, 3-oxobutanoate is formed by a reaction catalysed by β–ketoacyl-ACP synthetase, this is reduced to 3-hydroxy-butanoate by β–ketoacyl-ACP reductase, which is in turn dehydrated to *trans*-2-butenoate by β–hydroxyacyl-ACP hydratase before it is reduced to butanoate by enoyl-ACP reductase. The process then continues with the addition of a further six units of malonyl-ACP by successive cycles of these reactions until palmityl-ACP is formed. At this point, a thioesterase removes the fatty acyl product as the free acid (with the mammalian enzyme), and it must be converted to the CoA-ester before it can enter into the various biosynthetic pathways for the production of specific lipids. Medium-chain fatty acids are produced by enzymes in which the specificity of the thioesterase component differs from normal, i.e. the chain-elongation cycle is terminated prematurely. With the fungal fatty acid synthase, the finished acid is attached directly to CoA using a malonoyl/palmitoyl transacylase domain.

Palmityl-CoA can be further elongated by C_2 units to form long- or very-long-chain fatty acids by Type III fatty acid synthetases (elongases). Based on the presence of similar motifs in their gene structure, six enzymes, that have been termed ELOVL 1 to 6 (Elongation of very-long-chain fatty acid) and are believed to perform the condensation reaction in the elongation cycle, are recognized. Three of these (ELOVL 1, 3 and 6) are involved in the production of saturated and monoenoic fatty acids, while the remainder are elongases of polyunsaturated fatty acids. Some parasitic organisms produce all their fatty acids by using elongases. For example, *Trypanosoma brucei*, the human parasite that causes sleeping sickness, uses three elongases the first converting C_4 to C_{10}, the second extending C_{10} to C_{14}, and the third elongating C_{14} to C_{18}.

With odd-chain fatty acids, the primer molecule can be propanyl-CoA, but these can also be produced from even-numbered components by *alpha*-oxidation. Similarly, short- and medium-chain fatty acids can be produced as by-products of oxidative processes.

Type I fatty acid synthases are generally considered to be more efficient, because all the enzymatic activities are linked in a single polypeptide template from which the intermediates cannot easily diffuse. The product is largely the single fatty acid palmitate. In contrast, type II fatty acid synthases can produce many different products for cellular metabolism, including fatty acids of different chain lengths, and unsaturated, *iso-* and *anteiso*-methyl-branched, and hydroxy fatty acids. In addition, ACP-intermediates from the process, which are diffusible entities, can be used for production of other important cellular constituents, such as lipoic acid.

It has long been known that for activity the mammalian fatty acid synthases exists as a dimer, while the fungal isomer is hexameric, but the exact nature and requirement for the polymeric states was not known until X-ray crystal structures of the enzymes were obtained. With the mammalian enzyme, the two monomers are in a head-to-head arrangement (not head-to-tail as previously believed) and dimerization seems to be dictated by the structure of the β-ketoacyl synthase

domain, i.e. the component responsible for the key chain-elongation step. Although the structure of the fungal isomer is very different, it appears that the β-ketoacyl synthase domain is again the dominant factor controlling polymerization.

Of course, this account presents the basic details of the biosynthetic process only. Those requiring more detailed information are referred to the reading list below.

While saturated fatty acids obviously provide desirable properties to lipids in membranes by conferring rigidity where this is required, their nutritional value is a matter for debate, especially for those of medium chain-length. Most nutritionists recommend keeping dietary intakes of saturated fatty acids as low as possible, but detailed discussion of this topic is not possible here.

Recommended Reading

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o   Vance, D.E. and Vance, J. (Editors) *Biochemistry of Lipids, Lipoproteins and Membranes (4th Edition)*. (Elsevier, Amsterdam) (2002) – Several chapters.
o   White, S.W., Zheng, J., Zhang, Y.M. and Rock, C.O. The structural biology of type II fatty acid biosynthesis. *Annu. Rev. Biochem.*, **74**, 791-831 (2005).

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