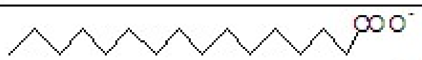
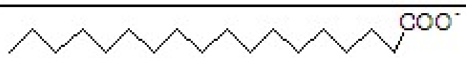
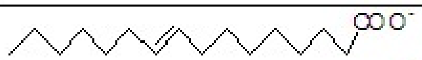
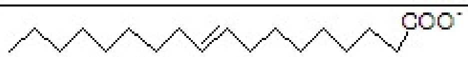
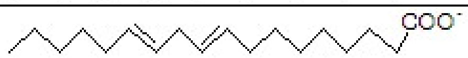
Catabolism of fatty acids and triglycerides

Fatty acids

- Fatty acids are long chain hydrocarbons having at one extremity a carboxylic acid functionality : R-COO^-.
- Fatty acids contains 10 to 24 carbon atoms, the most common are 16 or 18. Atom number is always pair.
- Fatty acids can be saturated or carry one or two instaurations.

Acides gras Saturés	
Acide palmitique (C_{16})	
Acide stéarique (C_{18})	
Acides gras Insaturés	
Acide palmitoléique	
Acide oléique	
Acide linoléique	

Catabolism of fatty acids
(Lynen Spiral)

- Lynen S. catabolize a fatty acid (2n+2 carbons) in n+1 acetate condensed on coenzyme A (HSCoA) :

$$CH_3\text{-}(CH_2)_{2n}\text{-}COO^- + (n+1)\ HSCoA \longrightarrow n+1\ CH_3COSCoA$$

- Lynen S. is located in the *mitochondria* with exception of the first reaction (that is not part of the spiral) : formation of R-CH_2-CH_2-COSCoA, this last reaction is located at the *cytosol*.
- Lynen S. starts by condensation of HSCoA on –COO^- giving R-CH_2-CH_2-COSCoA.
- A sequence of reactions transform R-CH_2-CH_2-COSCoA in CH_3COSCoA and R-COSCoA.
- The cycle is reputed until complete acetyl-CoA (CH_3COSCoA) degradation.

Predictable simple reactions (1 cycle)

In mitochondria :

- R-CH_2-CH_2-COSCoA + HSCoA → → → CH_3COSCoA + R-COSCoA

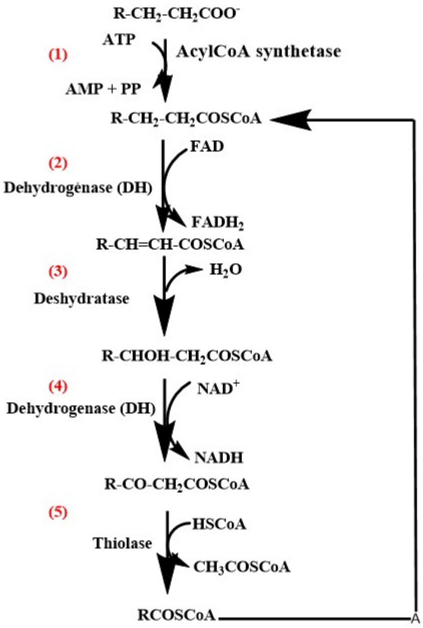
(In the first step condensation of SHCoA occurs)

Condensation	1
C-C Skeleton breakdown	1
Oxidation	2

Comment : Prevision of the number of simple reactions is simple and allows to analyze metabolism.

- 0 oxidation could correspond to an oxidation and a reduction.
- Several simple reaction can occur simultaneously in a same step.
- This calculation can not give the number of steps.

Lynen catabolism



Notes:

1 : AcylCoA is synthetized in the cytosol and the transported to the mitochondria in where lynen cycle occurs.
The mechanism is different in plants and animals.

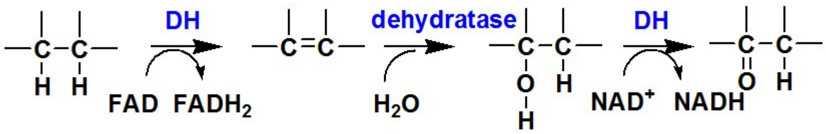
2 :
RCOSCoA is degraded always in the same way than R-CH_2-CH_2COSCoA. The same enzymes are involved

3 :
Condensation of HSCoA occurs only in the first step and not in all the cycle.

Biologic strategy for converting an alkane into aldehyde or ketone

- Many metabolisms use a classic sequence of reactions allowing the transformation of an alkane in an aldehyde or ketone : Lynen spiral, TCC (Krebs) metabolism of amino acids..

- The sequence is always the same :
  - Oxidation of an alkane in alkene : FAD-dependent (DH)
  - Hydration of the alkene to alcohol (dehydratase)
  - Oxidation of alcohol in aldehyde or ketone : NAD^+-dependent (DH)



- **Analyze of Lynen catabolism**

Principle

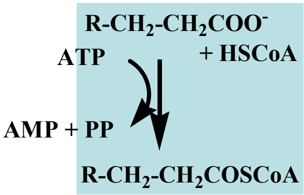
Analyze of metabolism (reading of the metabolism) involves:

- **Indicate the name or structure of substrates and products.**
- **Indicate the type(s) of simple reaction(s) involved.**
- **Indicate the name of the enzyme (enzyme group name or usual name).**
- **Indicate the involved coenzymes.**
- **Indicate reversibility.**

NB : It is possible that many metabolic pathways function in similar way. Thus, we can make previsions. However, although previsions are precious and strongly help in the study of metabolic pathways, only experimentation can give the exact metabolic pathway for a particular organism. This is because there are several variants between organisms.

Animal metabolism is now known. However, plant and other organism metabolism is not fully known because of complexity.

Step 1 (occurs only once in the cycle)



Acyl-CoA

Reaction type :	Condensation (DT)
Coenzyme :	HSCoA, ATP→AMP + PP (1)
Enzyme :	Acyl-CoA Ligase ou Acyl-CoA synthase
Energetics :	Irreversible

- Acyl-CoA is synthetized in cytosol and transported into the mitochondria in where the spiral takes place.

Comments :

1. This reaction allows polarization of the substrate in order to be oxidized.

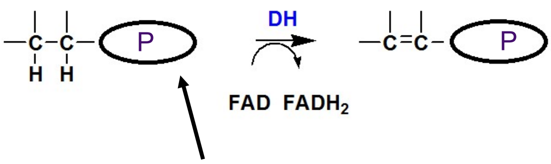
1. This condensation reaction requires energy, so we have ATP hydrolysis. However, AMP is produced and not ADP. This is exceptional.

Polarization by coenzymes

- In order to break a C-C bond or C-H bond, it is necessary to hava polarizing functions in the vicinity.

- The C-C or C-H bond must be in α or β position of the polarizing group.

If by itself a molecule is not enough polarized, we need a coactivator coenzyme in α.

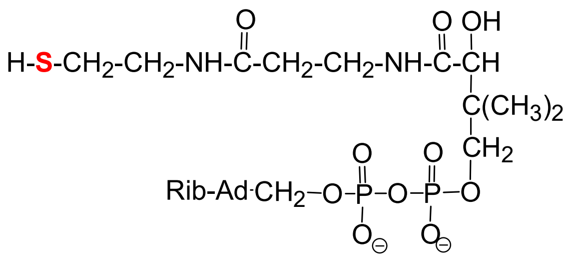


Polarizing function
or coenzyme

P can be -SCoA

Structure and role of Coenzyme A

- **Structure :**

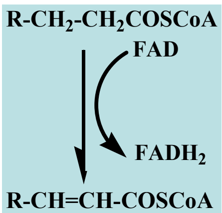


- **HSCoA can be condensed (by its thioester function) on carboxylates (substrates)**
- **Condensed -SCoA induces then an inductor effect that increases**
- **C-H and C-C bonds fragility in α position of the coenzyme carrying C.**
- **The C-C bond becomes more fragile**

- **The coenzyme A is known as un activator coenzyme**

Step 2 : Acyl-CoA → Enoyl-CoA

Acyl-CoA



Enoyl-CoA

Reaction type :	**Oxidation (1)**
Coenzyme :	**FAD (2)**
Enzyme :	**Dehydrogenase (DH)**
Energetics :	**Reversible**

Comments :

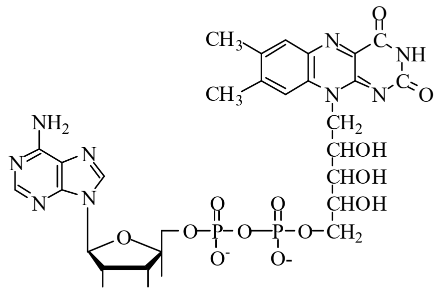
Oxidation of an alkane (C-C) a requires a polarized bond with mobile -H. –COOH function by itself is not enough polarizing (2 COOH could be ok).

Coenzyme A increases polarization and oxidation can occur.

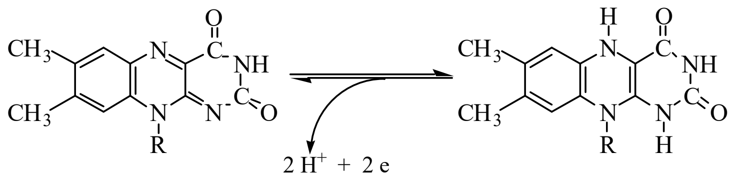
Oxidation of a alkane function (degree 0) into alkene (degree 1) requires always FAD.

Le FAD / $FADH_2$

- **Flaine adenine dinucleotide (FAD) is a REDOX coenzyme**



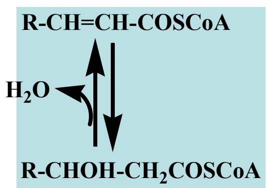
- **Mechanism :**



$$FAD + 2H^+ + 2e \rightleftharpoons FADH_2$$

Step 3 : Enoyl-CoA →Hydroxyacyl-CoA

Enoyl-CoA



Hydroxyacyl-CoA

Reaction type :	**Hydration**
Coenzyme :	***non* (1)**
Enzyme :	**Dehydratase (3)**
Energetics :	**Reversible (2)**

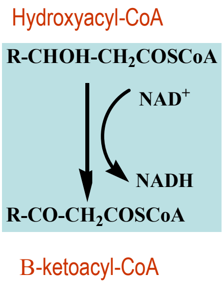
Comments :

1. **Hydration and dehydration reactions do not require coenzyme.**
2. **Hydration and dehydration reactions are always reversible.**
3. **The enzyme catalyze the reaction in the two sense The enzyme name is always dehydratase.**

Observation :

- **Hydration allows formation of alcohols that can then be oxidized into ketone.**

Step 4 : Hydroxyacyl-CoA → β ketoacyl-CoA



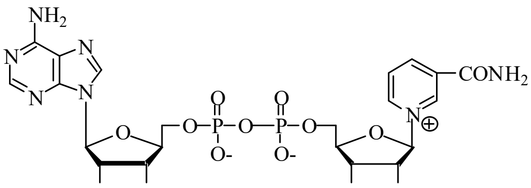
Reaction type :	**Oxidation (1)**
Coenzyme :	**$NAD^+ \rightarrow NADH$ (2)**
Enzyme :	**Dehydrogenase (DH)**
Energetics :	**Reversible**

Comments :

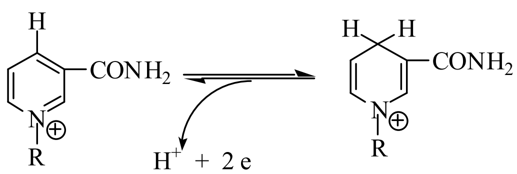
1. **This oxidation doesn't need activator having HSCoA present does not affect oxidation.**

$NAD^+/NADH$

- **Nicotinamide adenine dinucleotide (NAD^+) is a REDOX coenzyme:**



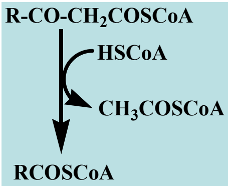
- **mechanism:**



$$NAD^+ + H^+ + 2\,e \rightleftharpoons NADH$$

Step 5 : β ketoacyl-CoA →Acyl-CoA + Acetyl-CoA

β-ketoacyl-CoA



Reaction type : **Coupled reaction :**
C-C Skelton breakdown (non REDOX**) (1)**
+ Condensation

Coenzyme : **HSCoA**

Enzyme : **Thiolase (2)**

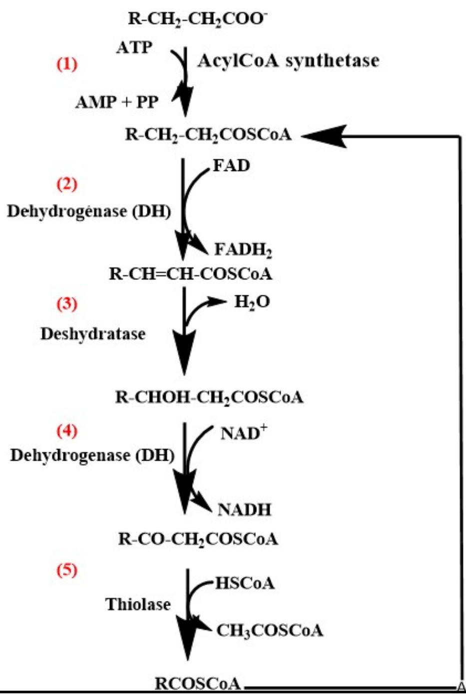
Energetics : **Reversible**

Comments :

1. **In general, synthesis/breakdown skeleton reactions are not REDOX in vivo.**

- **Breaking a C-C bond require it to be polarized.**
- **-COO^- is not enough to polarize α β positions.**
- **Coenzyme A (already there), is a good polarizing coenzyme**

2. **This reaction is called thiolyse (degradation under the effect of S)**



Substrate and energetic balances

This represent the balance of all steps in this metabolism (we don't consider water nor H^+), n = number of cycles .

First cycle :

$$\left\{\begin{array}{lll} CH_3(CH_2)_{2n}COO^- & \longrightarrow & CH_3(CH_2)_{2n-2}COSCoA + CH_3COSCoA \\ FAD + NAD^+ & & FADH_2 + NADH \\ 2\ HSCoA + 2\ H_2O & & \\ ATP & & AMP + 2\ P \end{array}\right.$$

Other cycles:

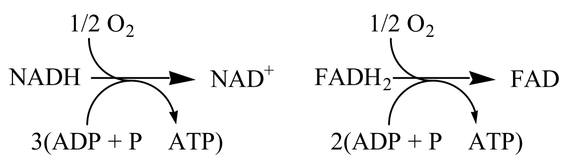
$$\left\{\begin{array}{lll} CH_3(CH_2)_{2n}COSCoA & \longrightarrow & CH_3(CH_2)_{2n-2}COSCoA + CH_3COSCoA \\ FAD + NAD^+ & & FADH_2 + NADH \\ HSCoA + H_2O & & \end{array}\right.$$

Global balance:

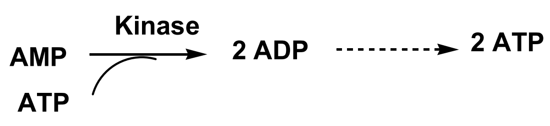
$$\left\{\begin{array}{lll} CH_3(CH_2)_{2n}COO^- & \rightarrow & n+1\ CH_3COSCoA \\ n+1\ HSCoA & & \\ n\ FAD + n\ NAD^+ & & n\ FADH_2 + n\ NADH \\ ATP & & AMP + 2\ P \\ n+1\ H_2O & & \end{array}\right.$$

Energetic balance

Balance in ATP considering respiratory chain



NB : AMP is regenrated though its transformation into ADP :



Therefore the hydrolysis of ATP into AMP requires 2 ATP

ATP balance

The ATP produced by lynen catabolism can be calculated for a fatty acid of 2n+2 carbons is degraded into acyl-CoA.

	Formed coenzymes	ATP produced
NADH	n	3 n
$FADH_2$	n	2 n
ATP*	-2	-2
Total		5n -2

* 1 ATP transformed into AMP is equivalent to 2 ATP consumed

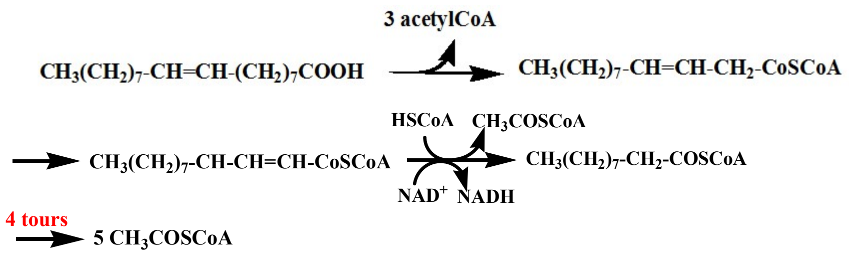
For intance, stearate (18 C, n=8) degradation into acetyl-CoA from 38 ATP

Catabolism of unsaturated fatty acids

Unsaturated fatty acid catabolism

For instance: oleic acid : ($CH_3(CH_2)_7$-CH=CH-$(CH_2)_7$COOH)

- Lynen catabolism occurs as in saturated fatty acid with the exception that the u nstauration results in economy of one FAD dependent oxidation :
- If the unsaturation is not well located for activation of the C-C bond (see bellow) an enoyl-CoA isomerase moves the double bond into C3:
  - $CH_3(CH_2)_7$-CH_2-CH=CH-COSCoA
- Lynen catabolism normaly continues:



ATP balance

example: oleic acid ($CH_3(CH_2)_7$-CH=CH-$(CH_2)_7$COOH)

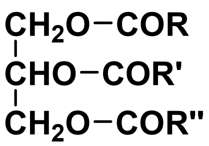
• When an unsaturation is involved one FAD is economized, we have 2 ATP less by insaturation.

• This fatty acid generates 36 ATP when converting to CH3COSCoA (9)

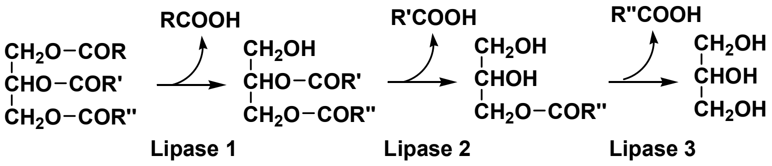
• In general each unsaturation produces 2 ATP less than the corresponding saturated fatty acid.

Catabolism of triglycerides (TG)

• TG are the fatty acids storage molecules that also store energy in the form of 3 fatty acids (equal or different)s) condensed to a glycerol molecule:



• TG degradation occurs by the hydrolysis of 3 different lipases (the enzymes are hydrolases, non condensation is here associated):



• *Glycerol catabolism is detailed in chapter « Glycolysis »*