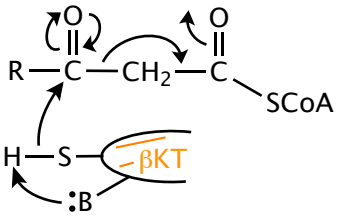
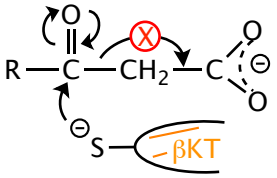
Session 15 - Chemical Interlude - Why did we have to use a thioester (FAcyl CoA)?

A

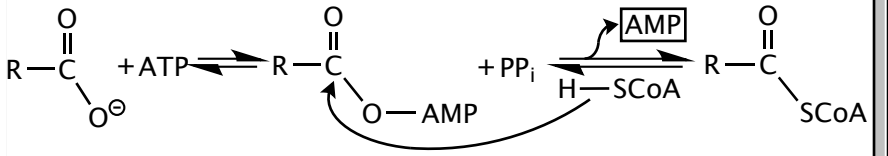
-- The reverse reaction (decarboxylation of β-keto acid) is VERY favorable.





Cannot do this with a carboxylic acid - unfavorable

Recall how to make a thioester from an acid:



Step I

Could phosphorylation work? - Probably.
AMP (and phosphate) are good leaving groups

Special Case 1 - FA has a Cis-Double bond

B

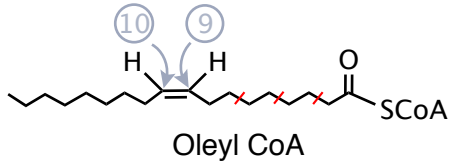
-- Cis-Double bonds promote membrane plasticity

-- trans-double bonds have a slight reduction in overall energy yield

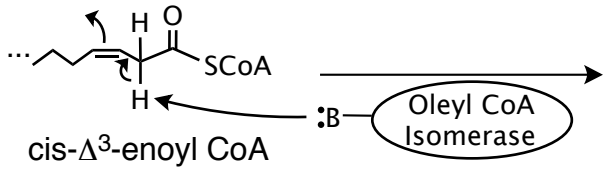
-- But, Cis-double bonds present a biochemical challenge to digestion

-- For example, Oleic Acid (18:1)Δ9

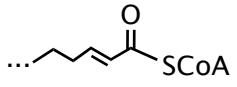
-- The word "oil" comes from oleic (olive oil = oleic)



Oleyl CoA



cis-Δ3-enoyl CoA



trans-Δ2 enoyl CoA

Hydratase

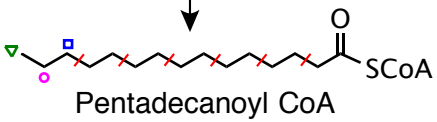
regular β-oxidation

Special Case 2 - Odd Chain FA: Introduction to Carboxylases

C

Pentadecanoic acid (15:0) = 1.2% of milk fat

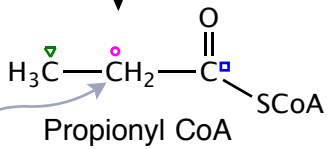
HSCoA
ATP



Pentadecanoyl CoA

6 Acetyl CoA

6 rounds of β-oxidation

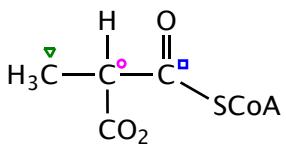


Propionyl CoA

"CO_2" inserted CH α-carbon; must activate CO_2 for it to add to Cα

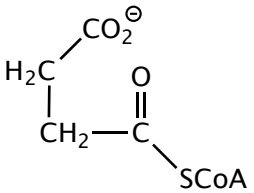
(Biotin)

Propionyl CoA Carboxylase



several steps

carbon skeleton rearrangement (Vitamin B_{12})



Succinyl CoA

TCA cycle

D

-- Odd chain FA in diet → Acetyl CoA (many) → Propionyl CoA (C–3)

Propionyl CoA (C–3) → "CO_2" → Succinyl CoA (C–4)

-- They are anapleurotic (increase rate of TCA cycle)

-- They can be gluconeogenic (later) ⇒ can result in net synthesis of glucose from this part of the FA chain (the Acetyl CoA-derived units are typically not gluconeogenic unless glyoxylate cycle (later) is operative)

-- The carboxylase family does much more than metabolize odd chain FA

More General View of Carboxylases

A

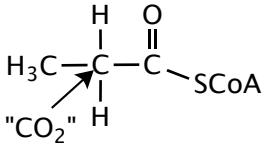
-- Require biotin (Vit. B_7), CO_2 and ATP

-- Increase size of molecule by one carbon (as "CO_2")

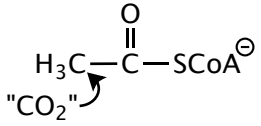
-- This is a kind of carbon fixation

-- Play a role in:

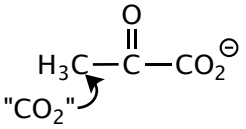
(a) Odd chain FA metabolism
Example: Propionyl CoA Carboxylase
* We'll look at this in detail later (this is also anapleurotic)



(b) FA biosynthesis
Example: Acetyl CoA Carboxylase



(c) Anapleurosis and Gluconeogenesis
Example: Pyruvate Carboxylase



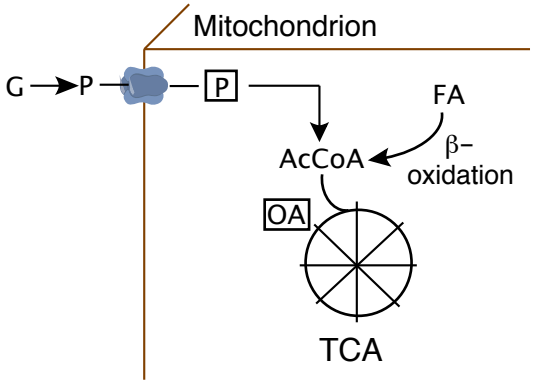
Start with (c) - Pyruvate Carboxylase (PC)

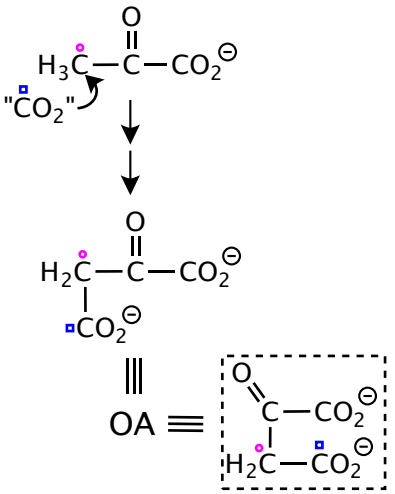
B

20

Role: To ↑ [Oxaloacetate] in mitochondrion → ↑ rate of TCA cycle

always limiting



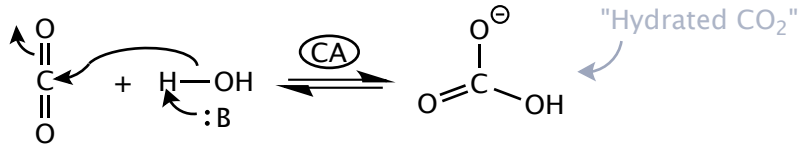


-- PC stimulated by AcCoA

-- This regulatory mechanism keeps rate of TCA matched to rate of generation of AcCoA

Steps (most are common to all carboxylases)

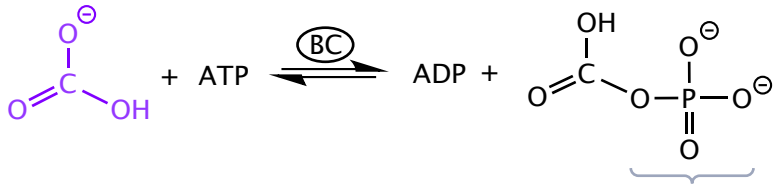
1.) Synthesis of Bicarbonate via Carbonic Anhydrase (CA)



not very soluble in water

very soluble

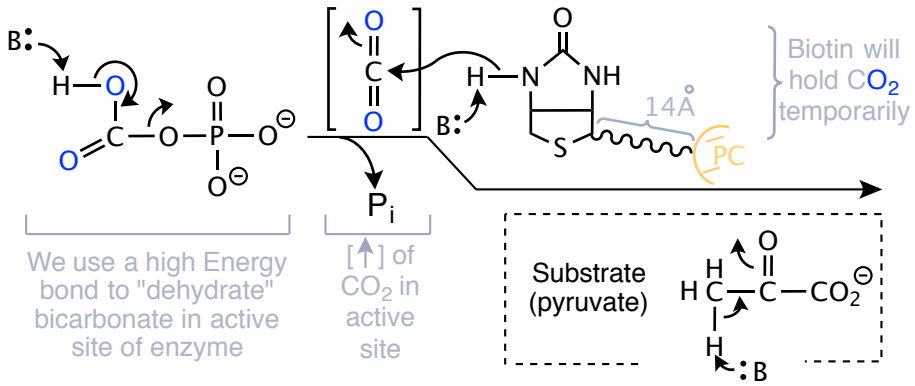
2.) Biotin Carboxylase (BC) Reaction of Pyruvate Carboxylase (PC)



carbonyl (or carboxy) phosphate

B

2 cont.) Biotin Carboxylase Reaction of Pyruvate Carboxylase (PC)

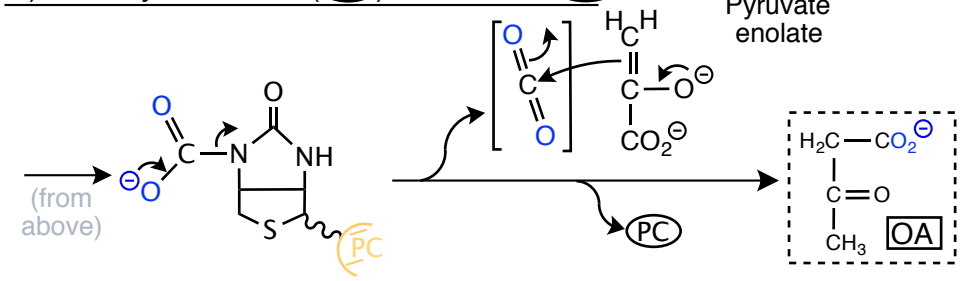


Biotin will hold CO_2 temporarily

We use a high Energy bond to "dehydrate" bicarbonate in active site of enzyme

[↑] of CO_2 in active site

3.) Carboxytransferase (CT) Reaction of PC



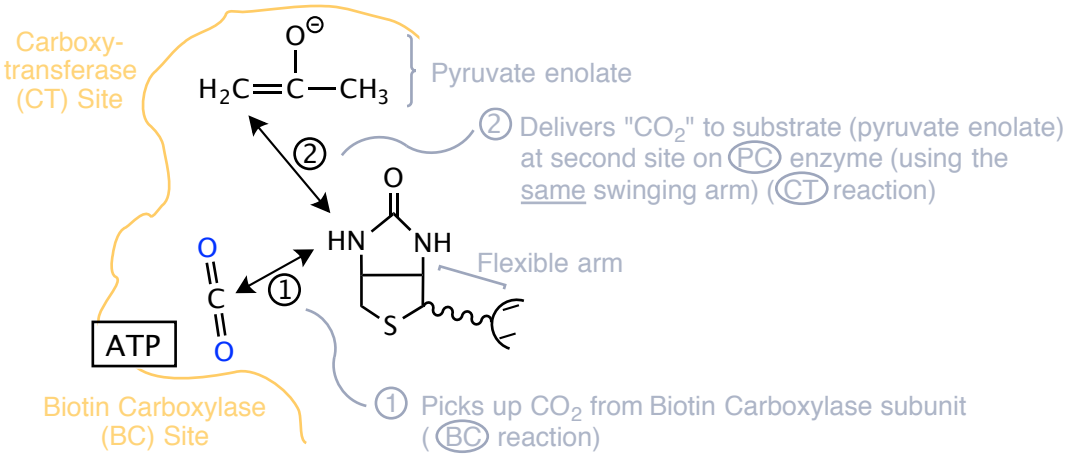
Pyruvate enolate

How to Visualize Carboxylase Chemistry

A

-- (CT) and (BC) are ~55Å apart

-- swinging arm does the "CO_2" transfer

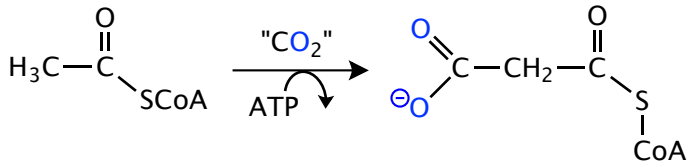


Example (b) - Acetyl CoA Carboxylase

B

22

-- Exactly the same chemistry, but acetyl CoA receives the CO_2



Malonyl CoA

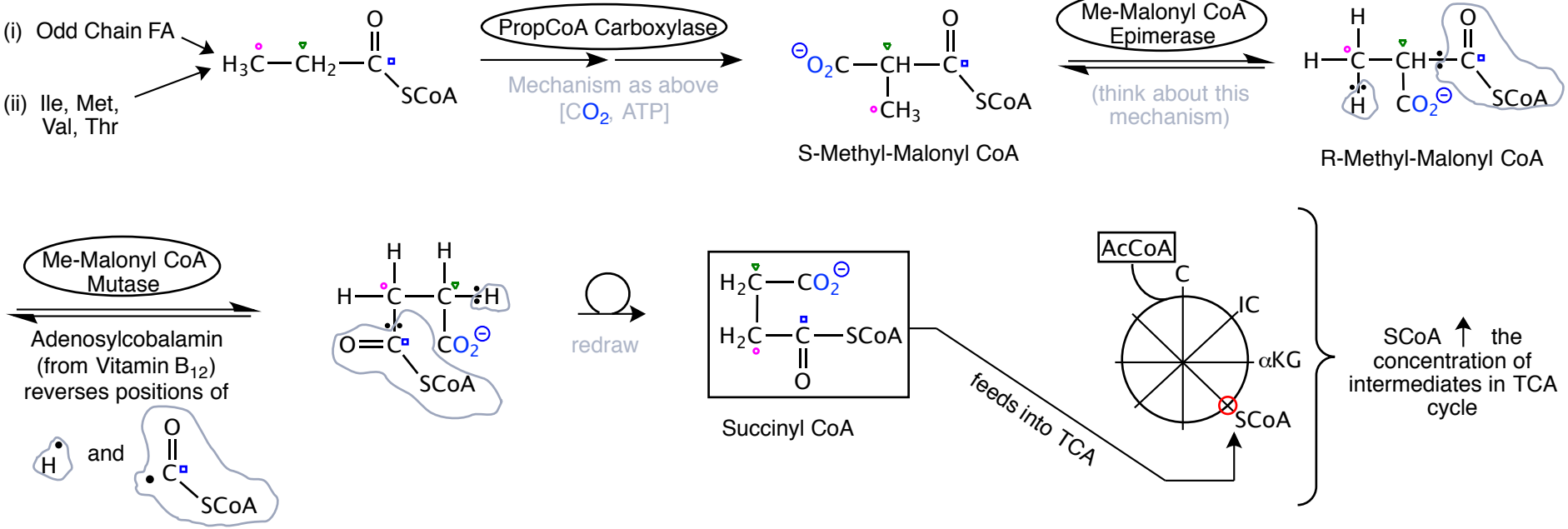
-- Malonyl CoA is the precursor to most of the ethylene units in FAs

-- We'll see this again soon when we talk about FA biosynthesis

Example (c) - Propionyl CoA Carboxylase - followed by synthesis of Succinyl CoA (2 more steps)

Introduced 2 pages back

C



5.07SC Biological Chemistry I
Fall 2013