

6 - Lipoic Acid

Lipoic Acid

Garrett/Grisham, Biochemistry with a Human Focus
Figure 14.28

(a)



Lipoic acid, oxidized form

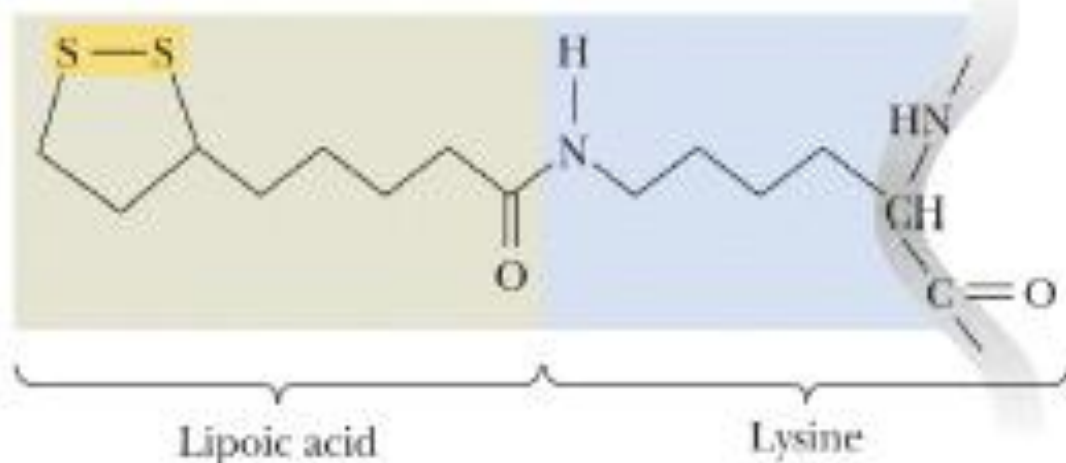
(b)



Reduced form

Redox reactions
Acyl carrier

(c)



Lipoic acid

Lysine

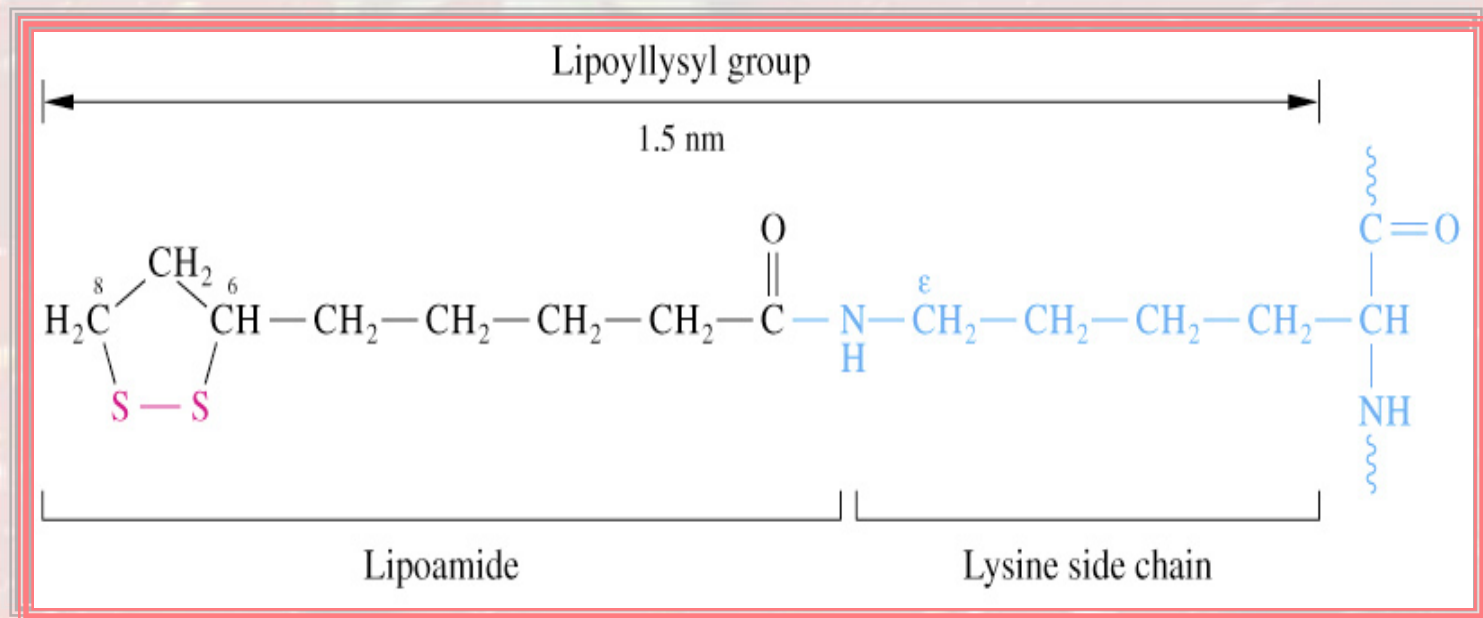
Lipoamide complex

Lipoamide

- ❖ Coenzyme lipoamide is the protein-bound form of lipoic acid
- ❖ Animals can synthesize lipoic acid, it is not a vitamin
- ❖ Lipoic acid is an 8-carbon carboxylic acid with sulfhydryl groups on C-6 and C-8
- ❖ Lipoamide functions as a “swinging arm” that carries acyl groups between active sites in multienzyme complexes

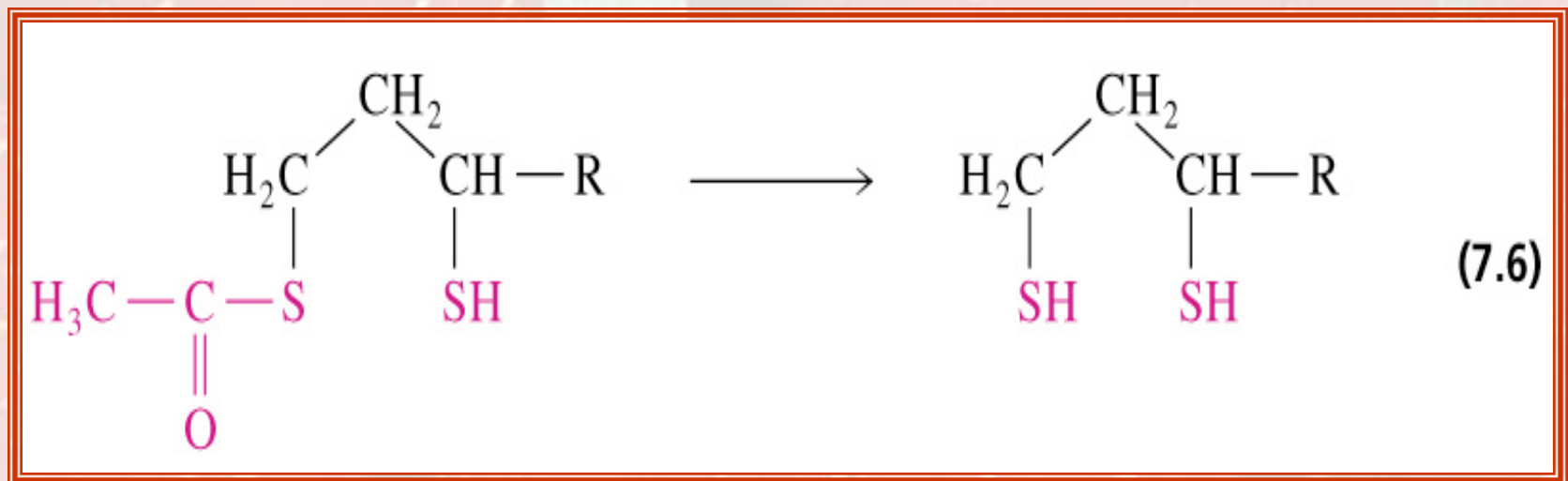
Lipoamide

- Lipoic acid is bound via an amide linkage to the ε-amino group of an enzyme lysine
- Reactive center of the coenzyme shown in red



Transfer of an acyl group between active sites

- ✓ Acetyl groups attached to the C-8 of lipoamide can be transferred to acceptor molecules
- ✓ In the pyruvate dehydrogenase reaction the acetyl group is transferred to coenzyme A to form acetylSCoA

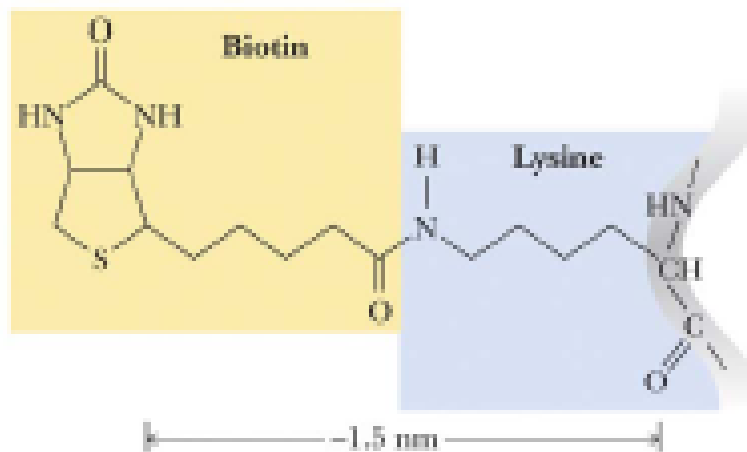


The background of the slide is a close-up photograph of several ripe, red strawberries. The strawberries are covered in small, yellowish-brown seeds (achenes) and have a slightly glossy texture. The lighting is soft, highlighting the natural color and texture of the fruit.

7- Biotin

Biotin

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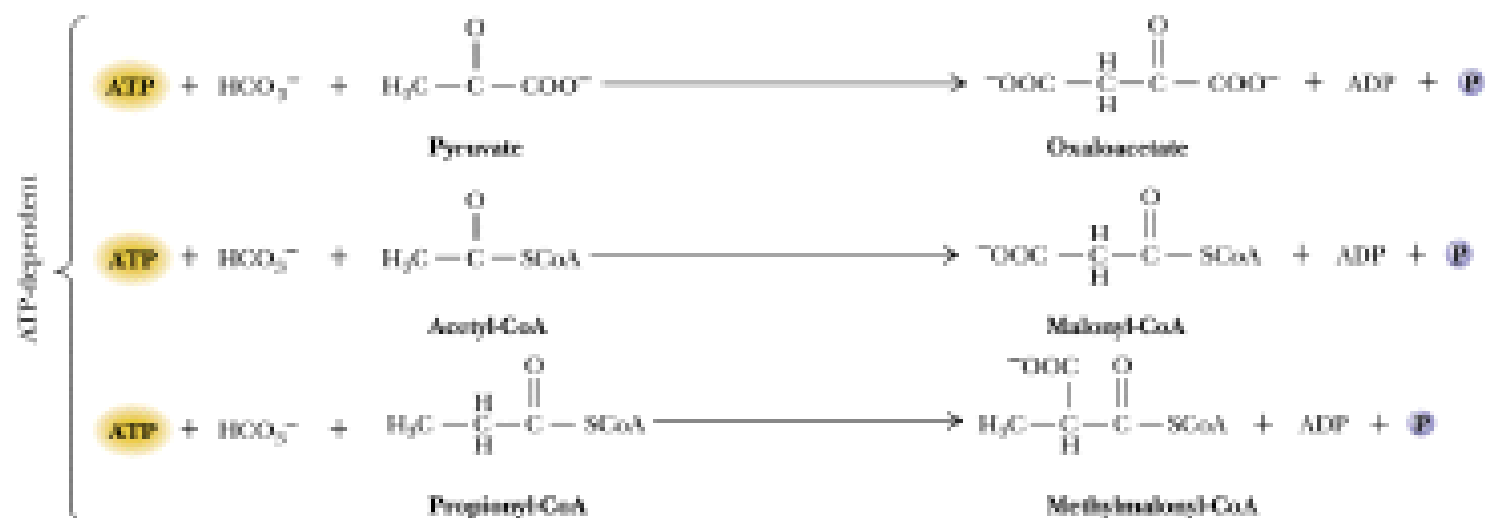


The biotin-lysine (biocytin) complex

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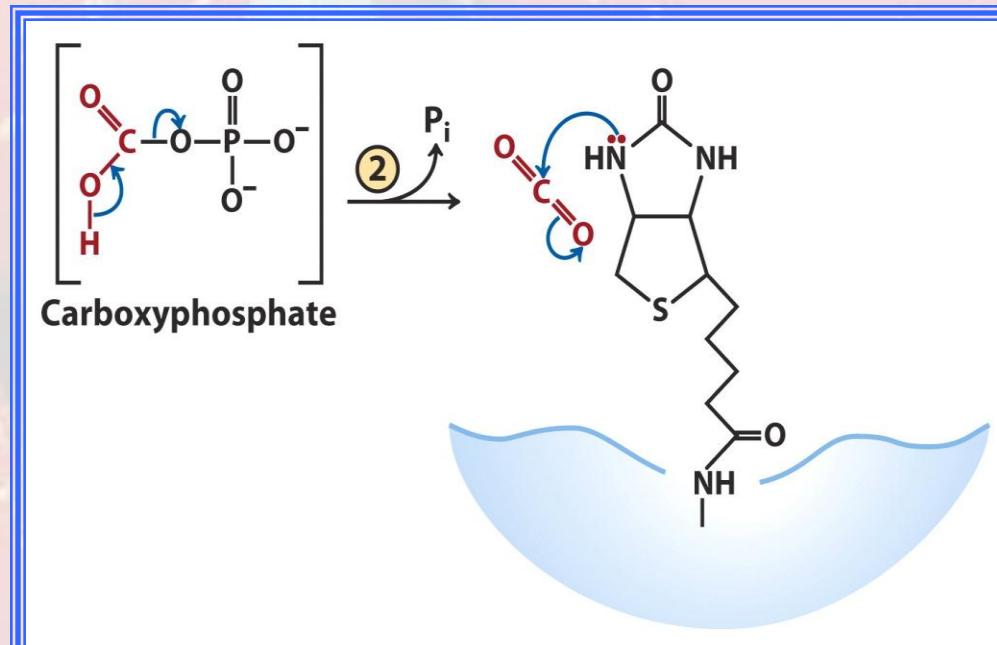
Long tether allows biotin to
Pick up carboxylate groups in one place
Use them in another

Table 14.5 Principal Biotin-Dependent Carboxylations



Biotin

- A water-soluble vitamin
- Biotin can be obtained from a variety of foods
- Deficiency is rare, but can result from a diet rich in raw eggs, because eggs are rich in avidin, which binds biotin very tightly
- A specialized carrier of one-carbon groups in the form of CO_2
- Example: Prosthetic group for pyruvate carboxylase

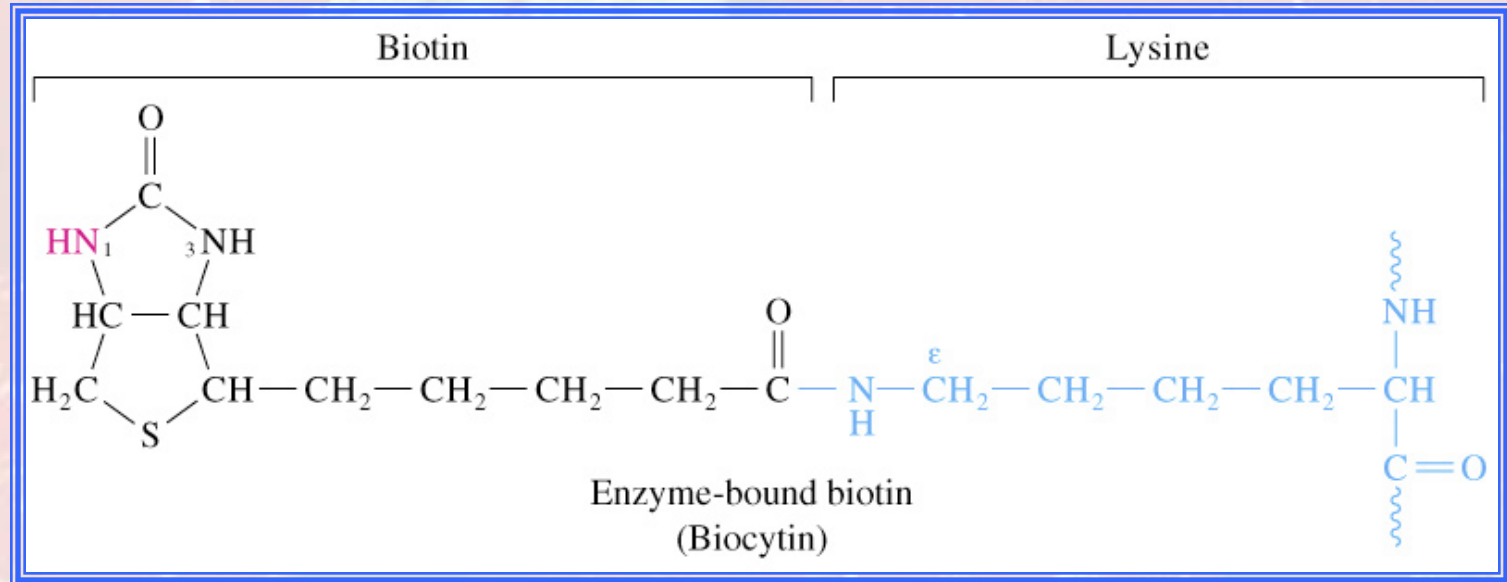


Biotin

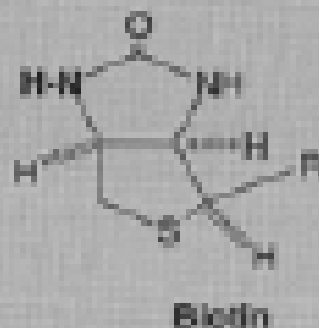
- ❖ Biotin is required in very small amounts because it is available from intestinal bacteria
- ❖ Avidin (raw egg protein) binds biotin very tightly and may lead to a biotin deficiency (cooking eggs denatures avidin so it does not bind biotin)
- ❖ Biotin (a prosthetic group) enzymes catalyze:
 - ❖ (1) **Carboxyl-group transfer reactions**
 - ❖ (2) **ATP-dependent carboxylation reactions**

Enzyme-bound biotin

- ❖ Biotin is linked by an amide bond to the ε-amino group of a lysine residue of the enzyme
- ❖ The reactive center of biotin is the N-1 (red)



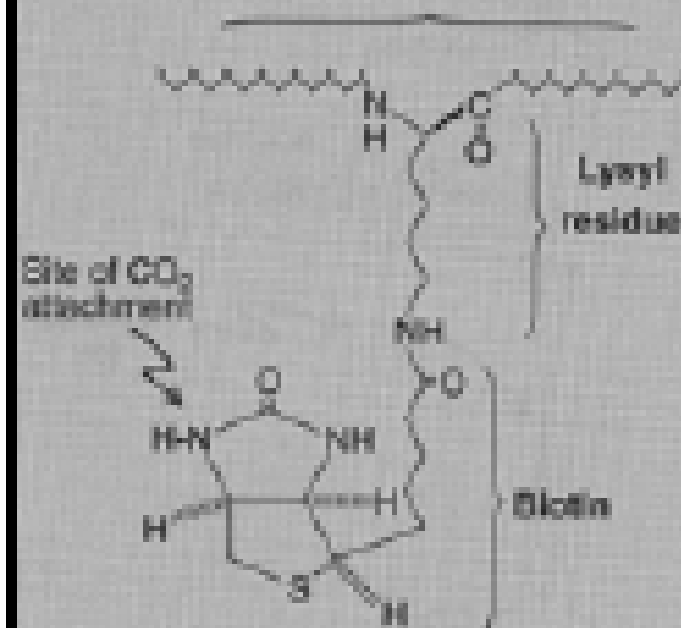
A



Speaking of Carboxylation: Biotin - no cool vitamin name

B

Protein portion of enzyme:
acetyl carboxylase
propionyl carboxylase
pyruvate carboxylase



Biotin bound to an enzyme

- Used in Carboxylation reactions
- Human requirement is met by synthesis from intestinal bacteria.
- Deficiencies can occur when :
 - You eat too many raw eggs
 - Take too much antibiotics.

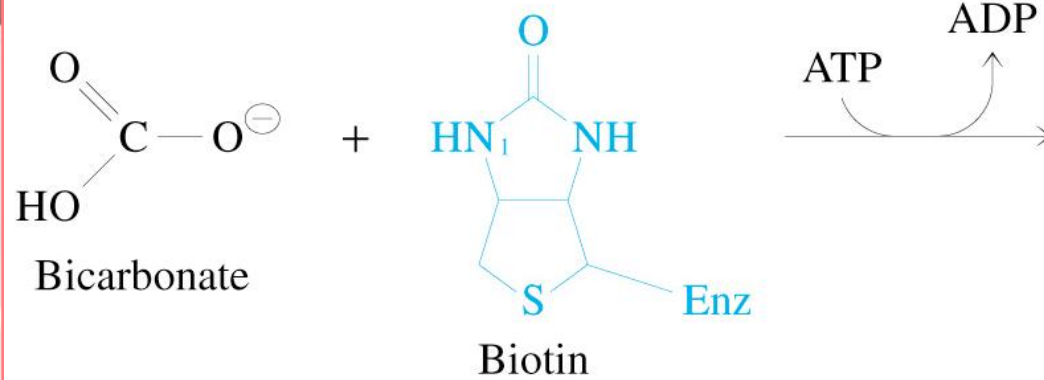
Symptoms include: Depression,
Hallucinations, Muscle pain, Dermatitis

Reaction catalyzed by pyruvate carboxylase

Two step mechanism

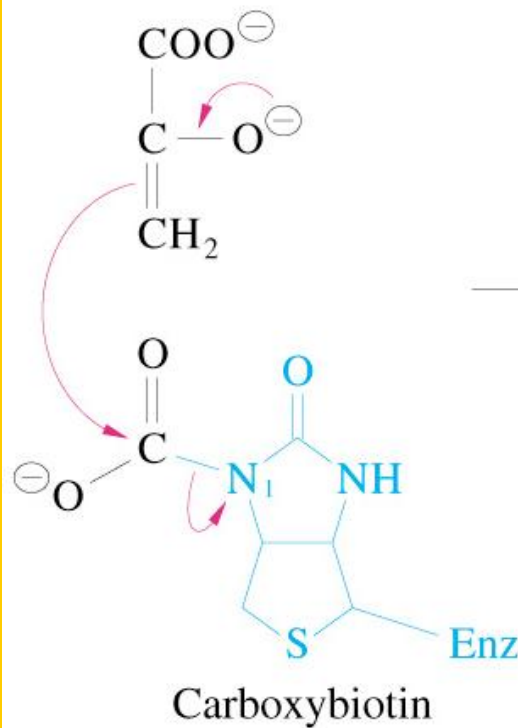
Step 1: Formation of carboxybiotin-enzyme complex (requires ATP)

Step 2: Enolate form of pyruvate attacks the carboxyl group of carboxybiotin forming oxaloacetate and regenerating biotin

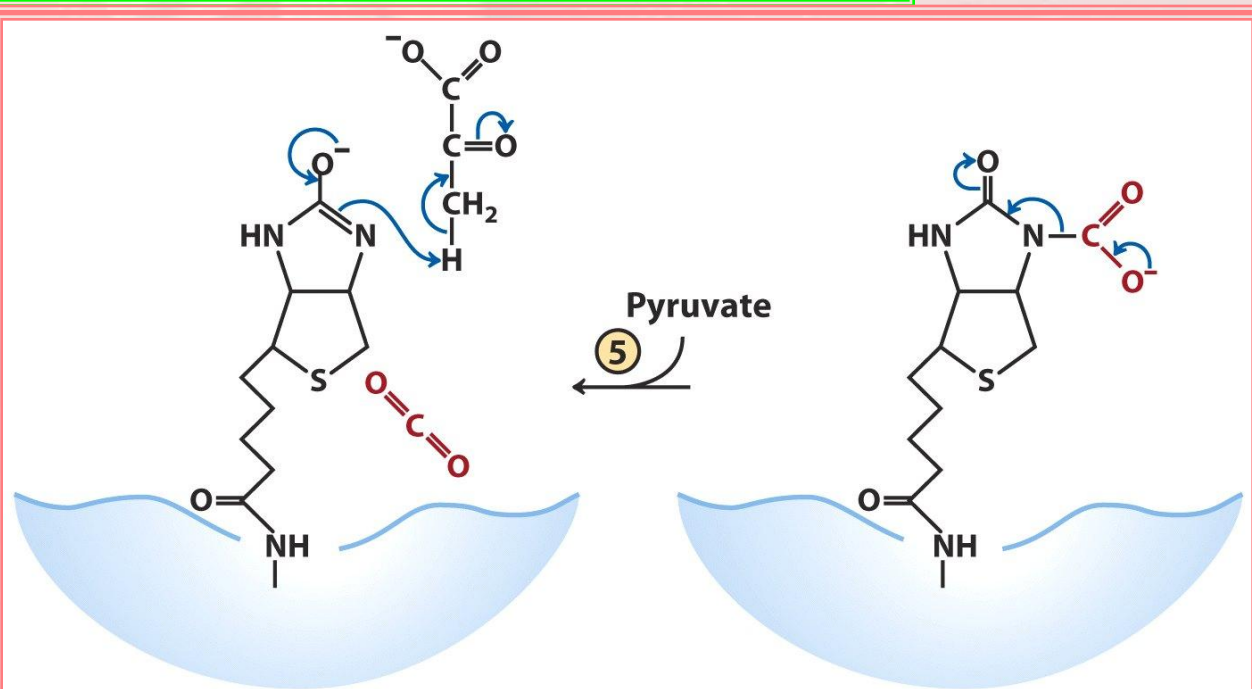
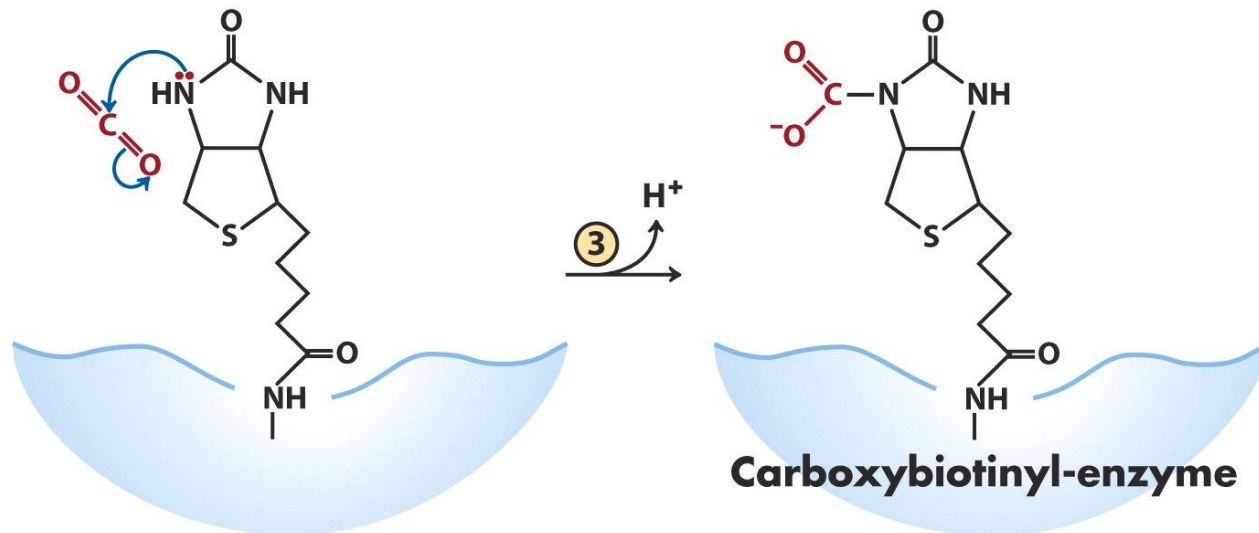


Enol pyruvate

Oxaloacetate



Biotin



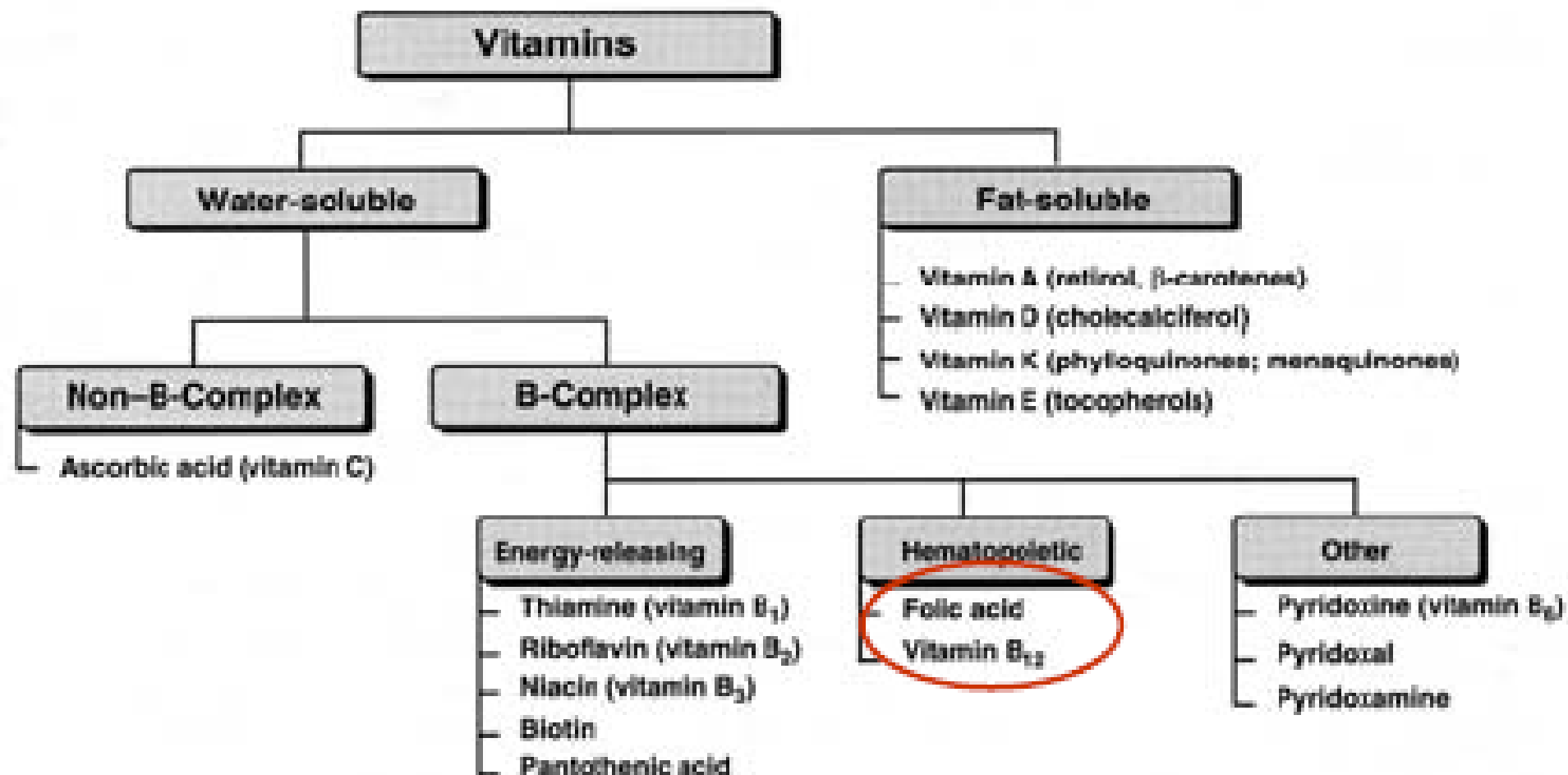
The background of the slide is a close-up photograph of several ripe, red strawberries. The strawberries are covered in small, yellowish seeds (achenes) and have a slightly textured surface. The lighting is soft, highlighting the natural color and texture of the fruit.

8. *Folic Acid*

Folic acid and vitamin B₁₂

Folate: green leafy vegetables, liver, lima beans, whole grains

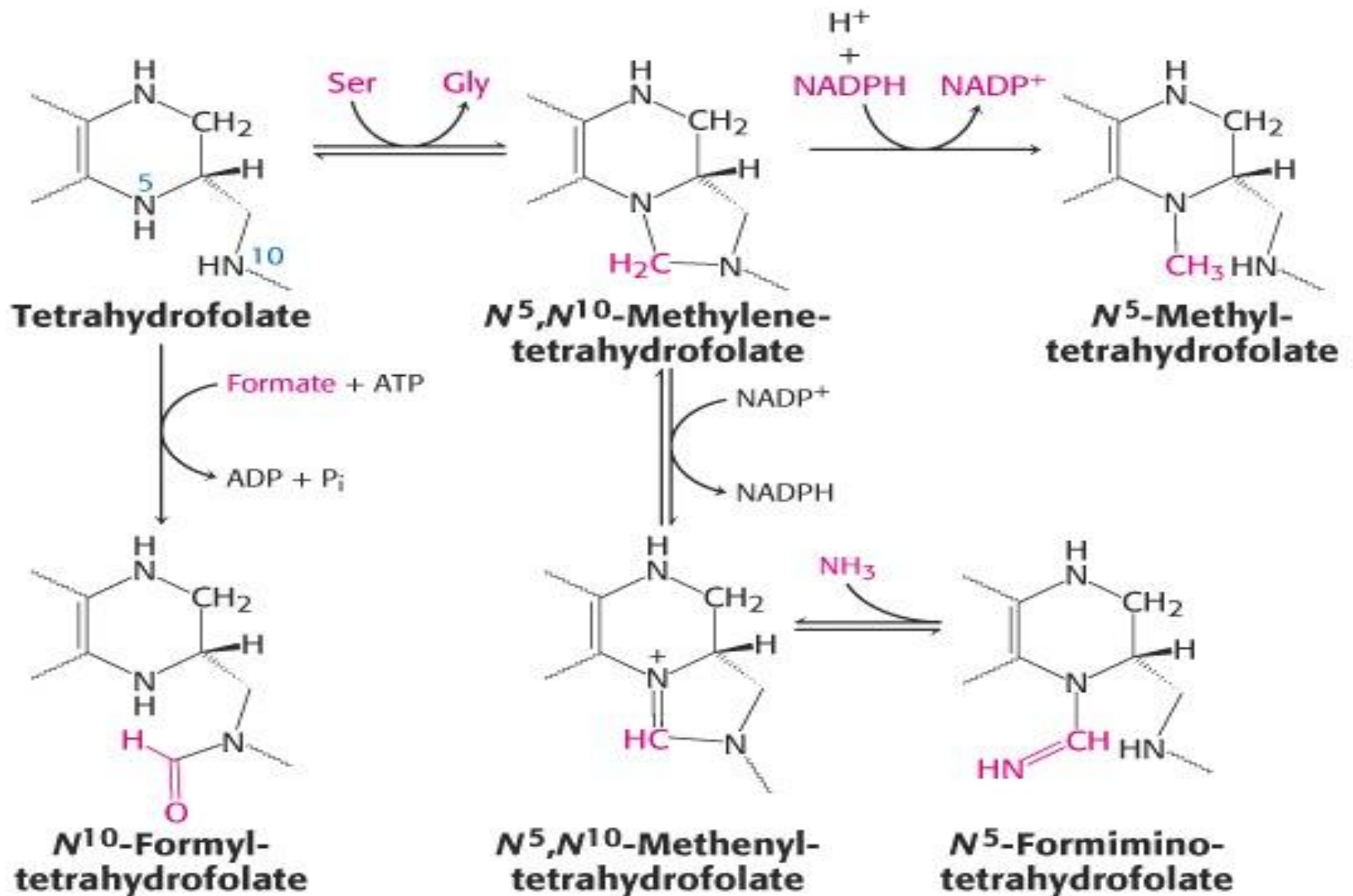
B₁₂: liver, whole milk, eggs, oysters, shrimp, pork, chicken



Folic acid

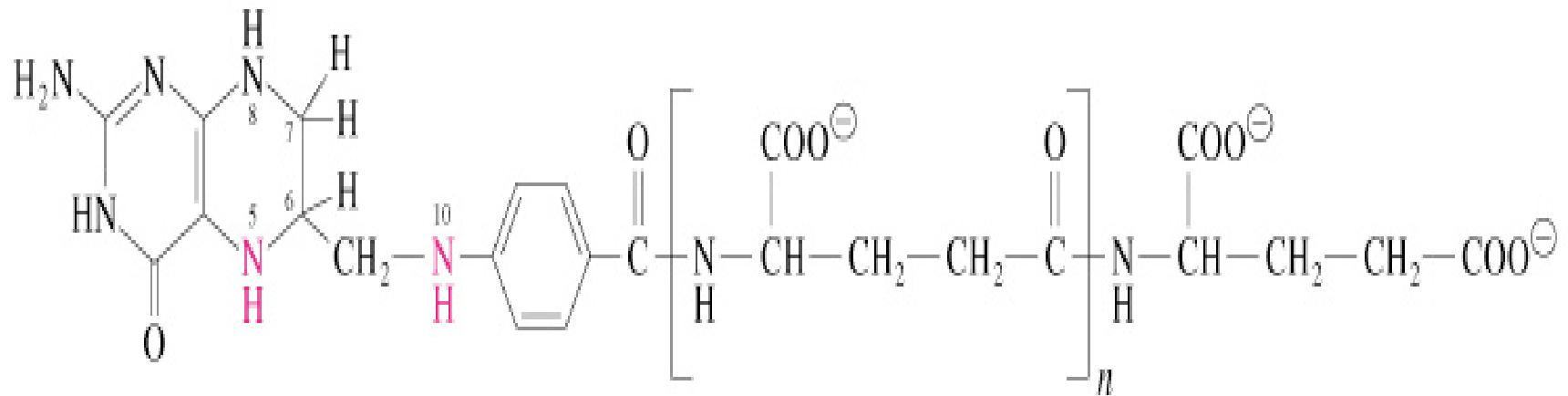
- ❖ Folic acid is found in leafy vegetables, beans and peas.
- ❖ Grains are now (since 1996) enriched with folic acid
- ❖ Prevents neural tube defects in the developing fetus, and heart disease
- ❖ The folic acid derivative tetrahydrofolate carries 1-carbon units...

Folic acid



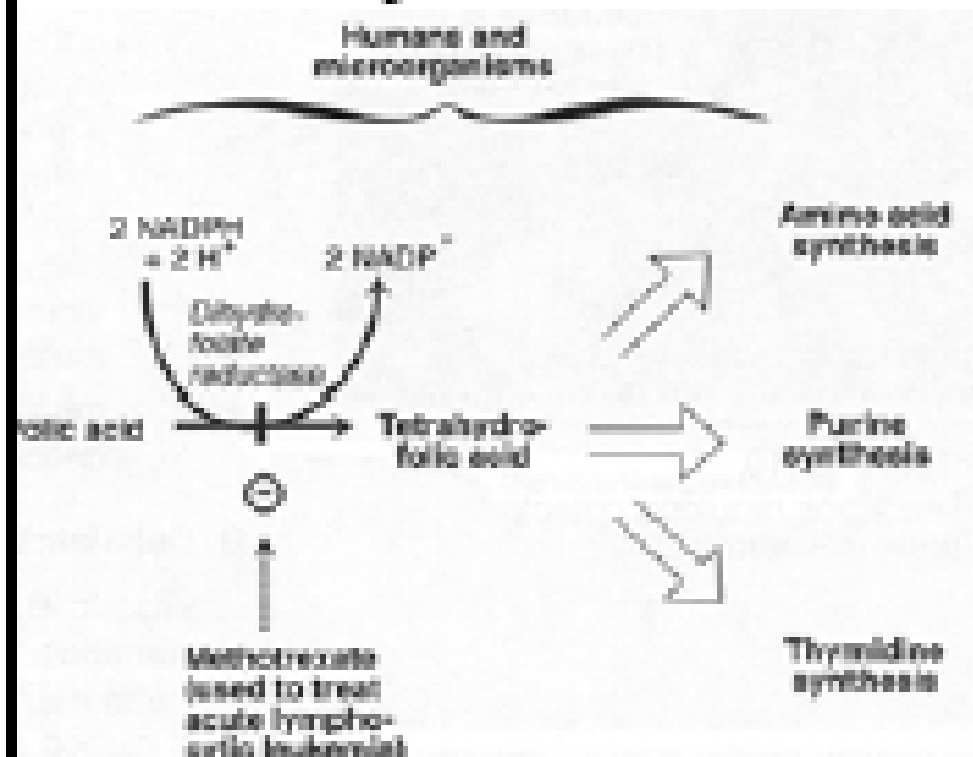
Pterin, folate and tetrahydrofolate (THF)

(c)



Tetrahydrofolate (Tetrahydrofolyl polyglutamate)

Need your folate for DNA synthesis.



Biosynthesis of serine, methionine, glycine, choline: but you can often get these from your diet.

Biosynthesis of the purine nucleotides: But you can salvage used nucleotides for this.

Biosynthesis of dTMP: That's the clincher - can't make DNA without folate.

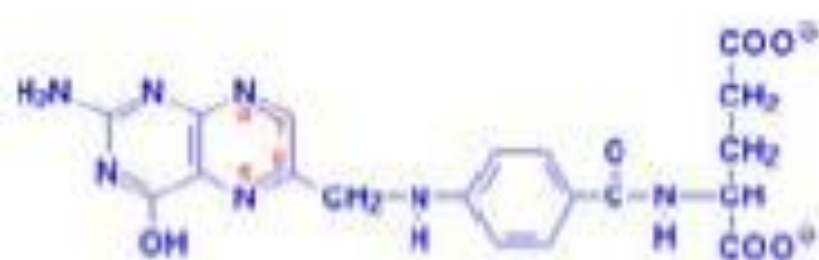
Deficiency causes anemia: DNA synthesis block.

Usually not a problem except in pregnant women.

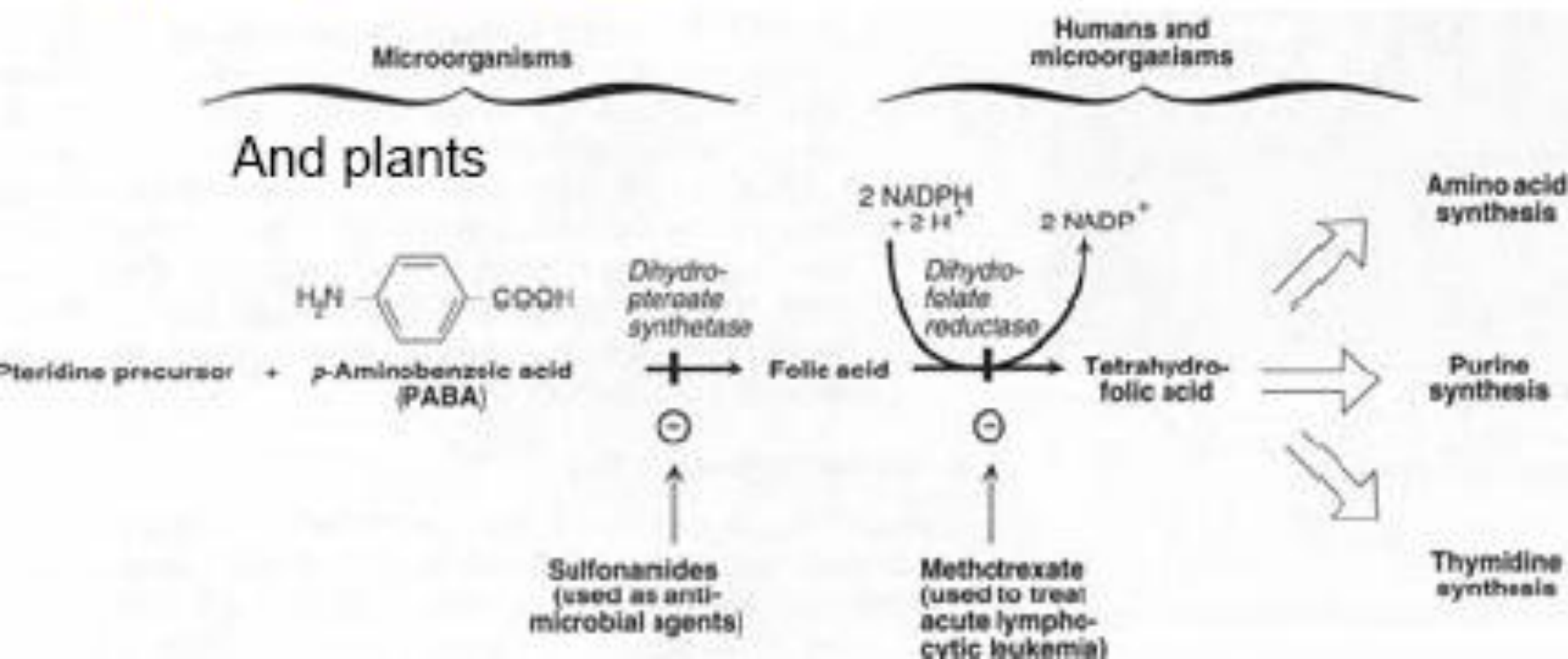
Tetrahydrofolate (THF)

- ❖ Vitamin folate is found in green leaves, liver, yeast
- ❖ The coenzyme THF is a folate derivative where positions 5,6,7,8 of the pterin ring are reduced
- ❖ THF contains 5-6 glutamate residues which facilitate binding of the coenzyme to enzymes
- ❖ THF participates in transfers of one carbon units at the oxidation levels of methanol (CH_3OH), formaldehyde (HCHO), formic acid (HCOOH)

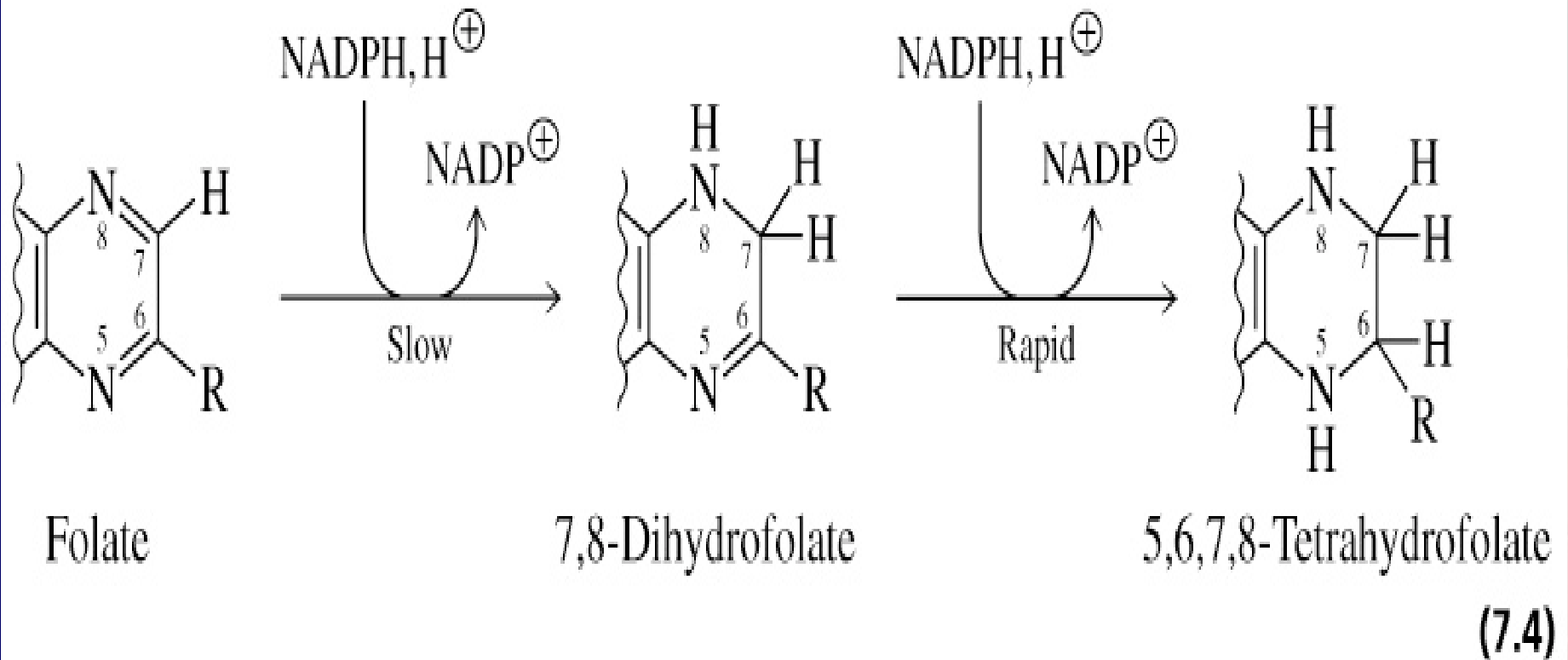
THF and DHF are made from Folate (Folic Acid)



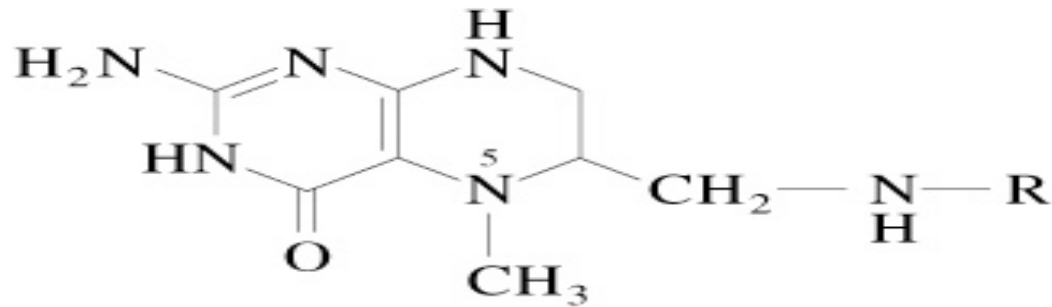
Used in One-Carbon Chemistry
Animals cannot synthesize it.



Formation of Tetrahydrofolate (THF) from folate

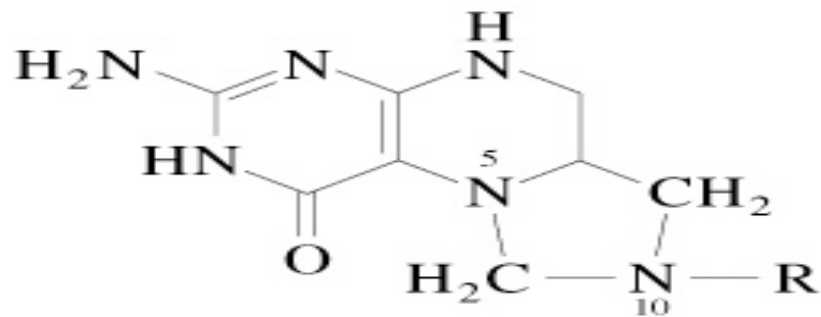
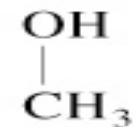


Oxidation level



5-Methyltetrahydrofolate

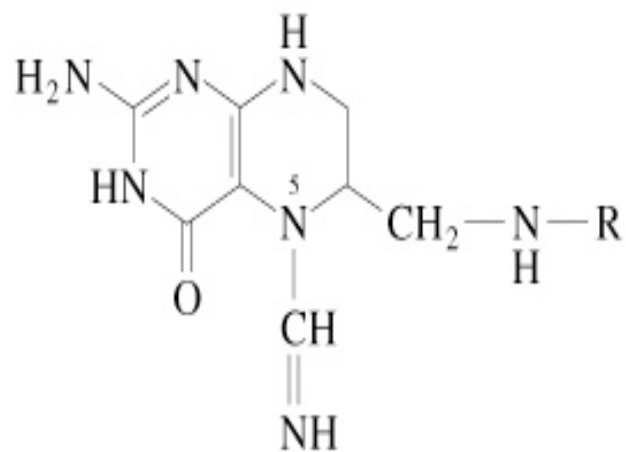
Methanol



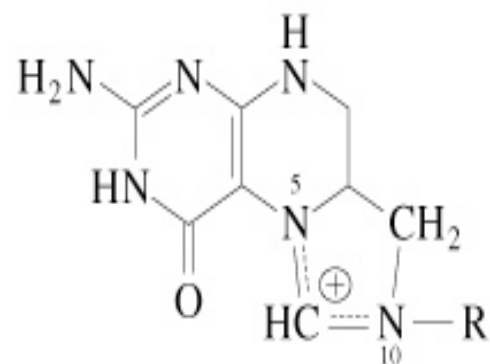
5,10-Methylenetetrahydrofolate

Formaldehyde



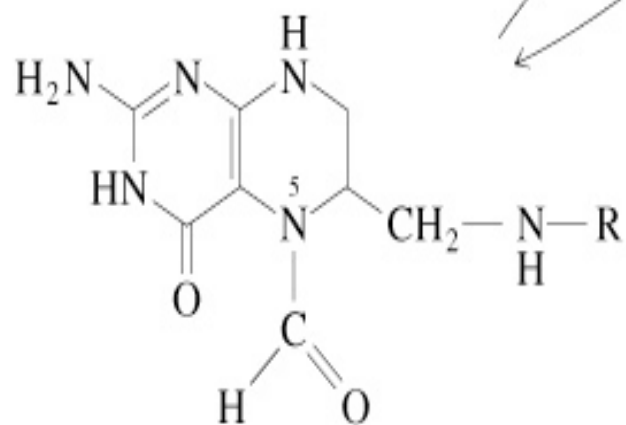
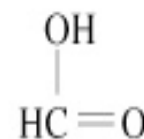


5-Formiminotetrahydrofolate

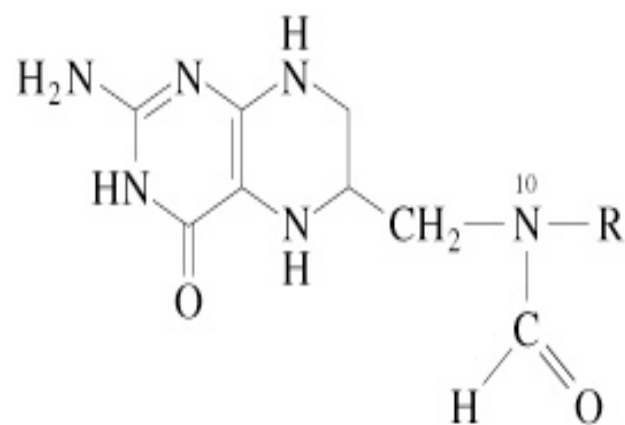


5,10-Methenyltetrahydrofolate

Formic acid



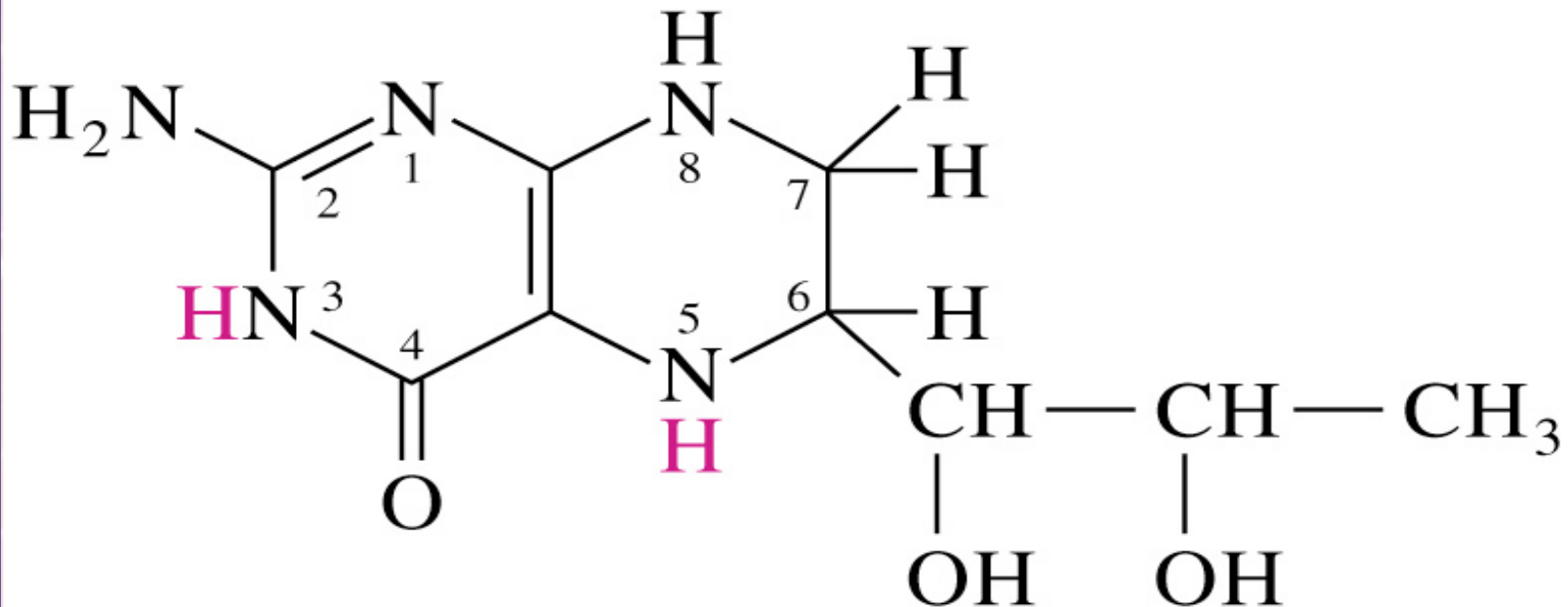
5-Formyltetrahydrofolate



10-Formyltetrahydrofolate

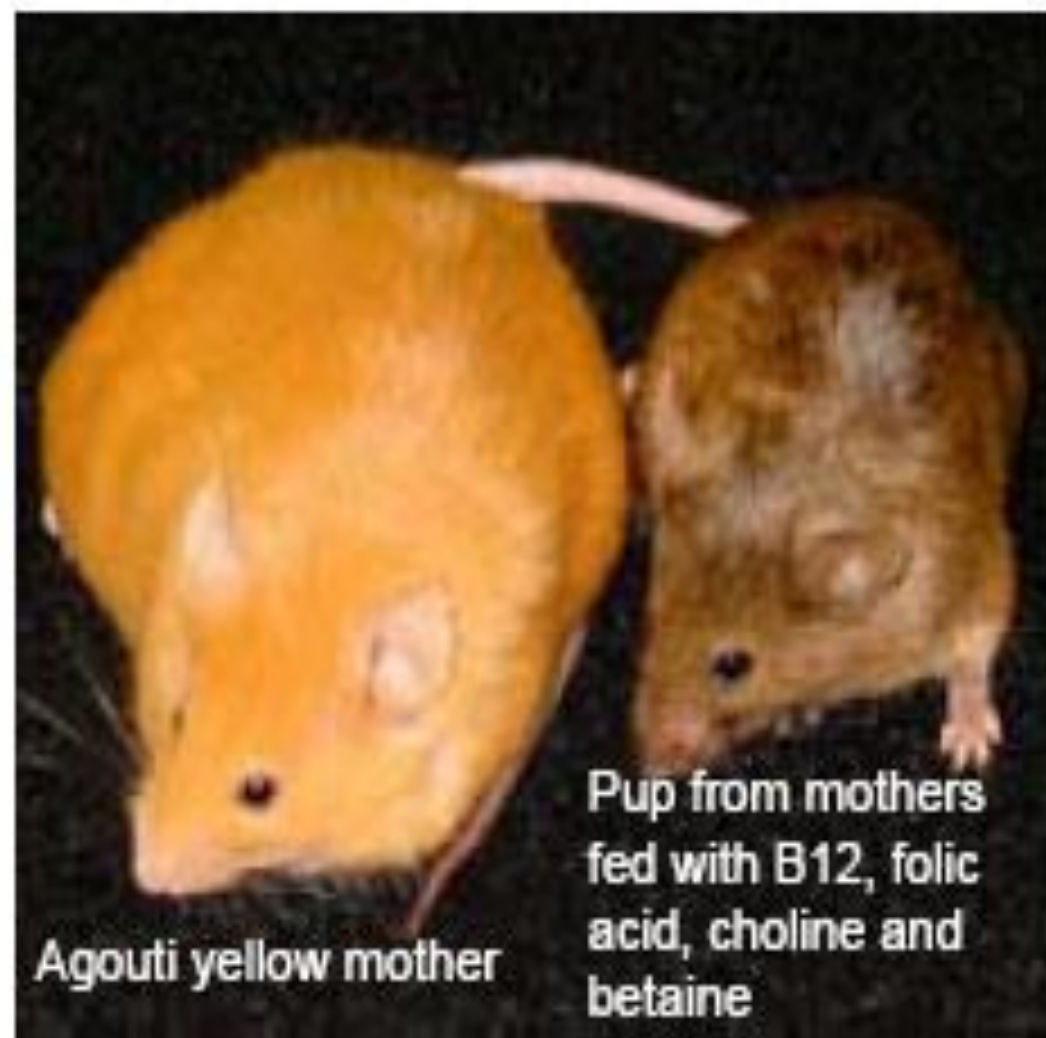
5,6,7,8, **Tetrahydrobiopterin**, a pterin coenzyme

- ❖ Coenzyme has a 3-carbon side chain at C-6
- ❖ Not vitamin-derived, but synthesized by some organisms



Folate and epigenetic regulation

Control
litters looked
like mother.



The pup's
Agouti gene
had same
sequence as
mother's but
was more
methylated.

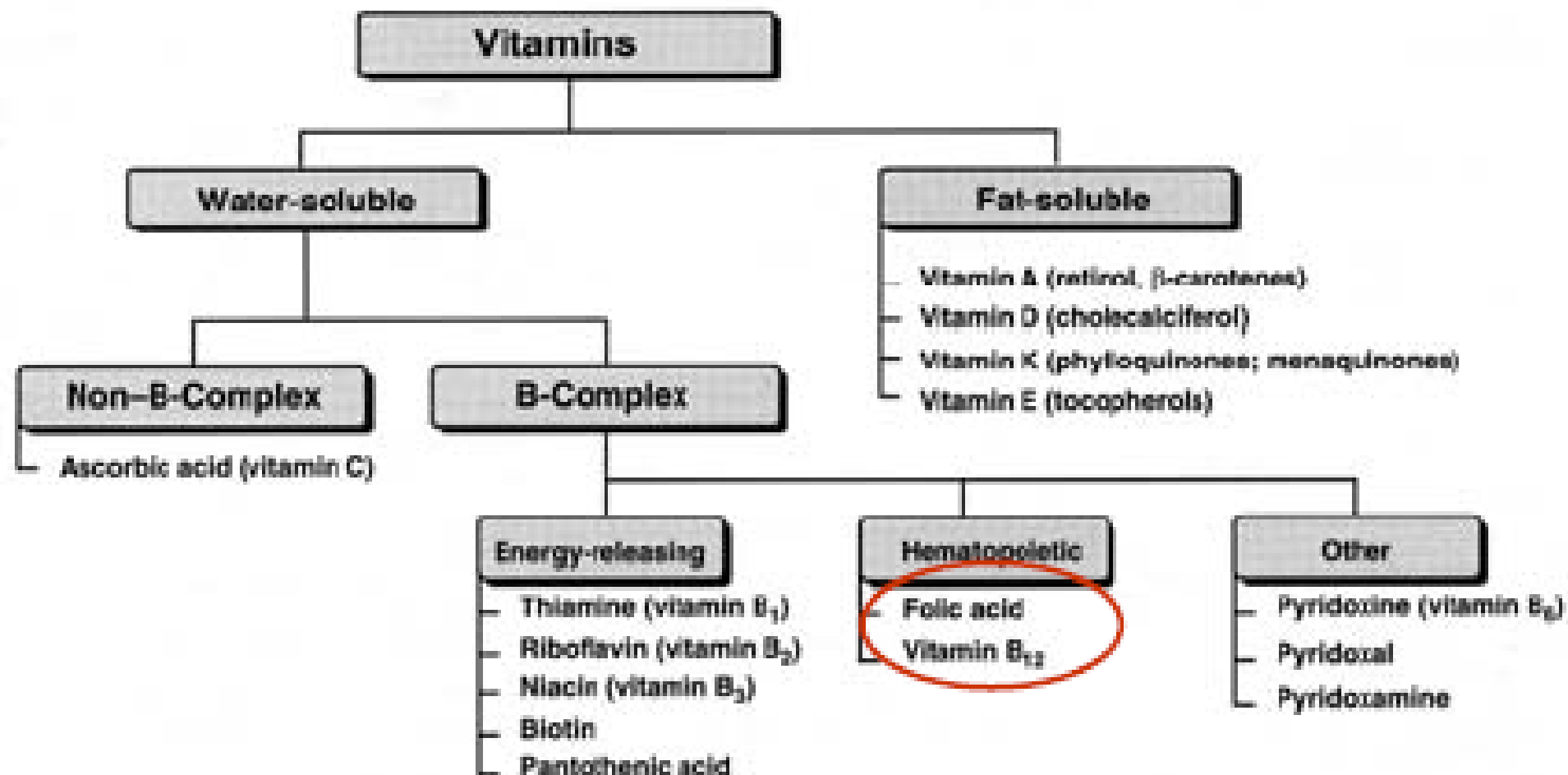
The background of the slide is a close-up photograph of several ripe, red strawberries. The strawberries are covered in small, light-colored seeds and have green leafy tops. The image is slightly out of focus, creating a soft, naturalistic backdrop for the text.

9. Vitamin B12

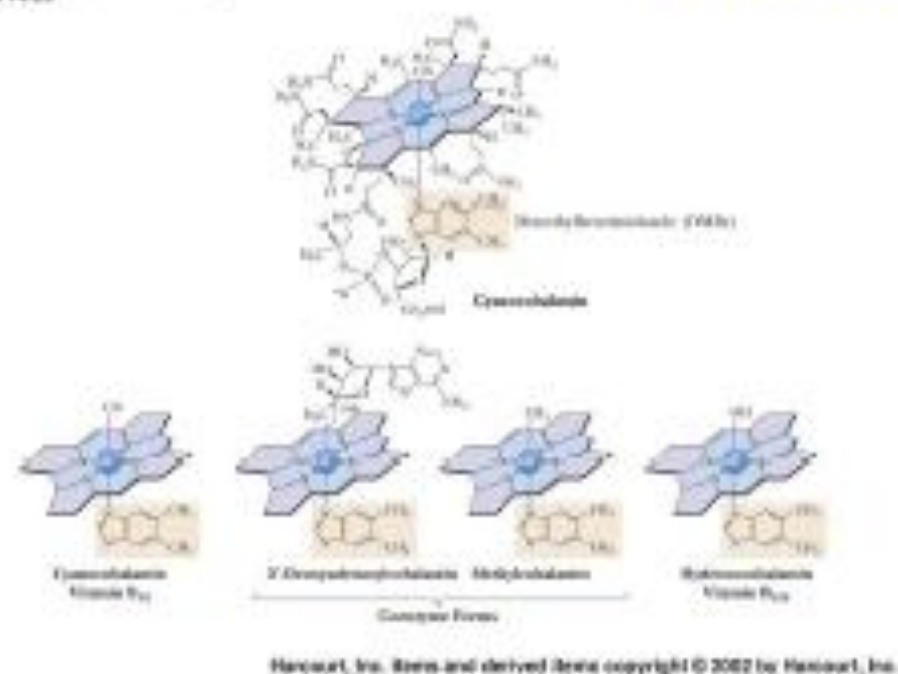
Folic acid and vitamin B₁₂

Folate: green leafy vegetables, liver, lima beans, whole grains

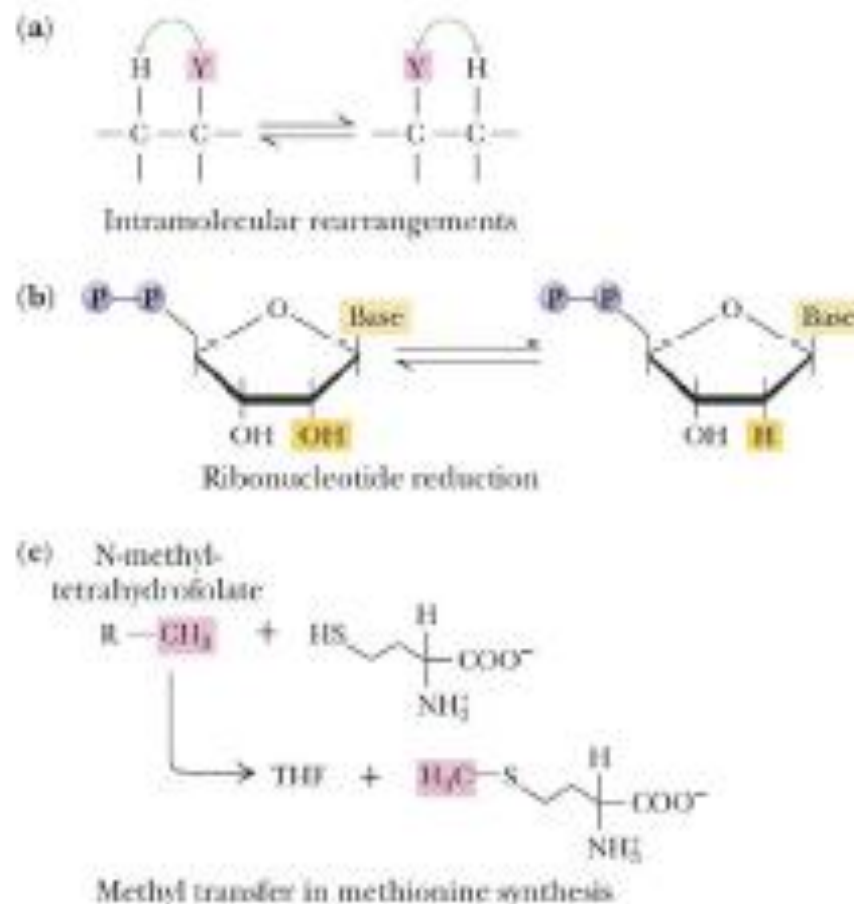
B₁₂: liver, whole milk, eggs, oysters, shrimp, pork, chicken



Vitamin B12

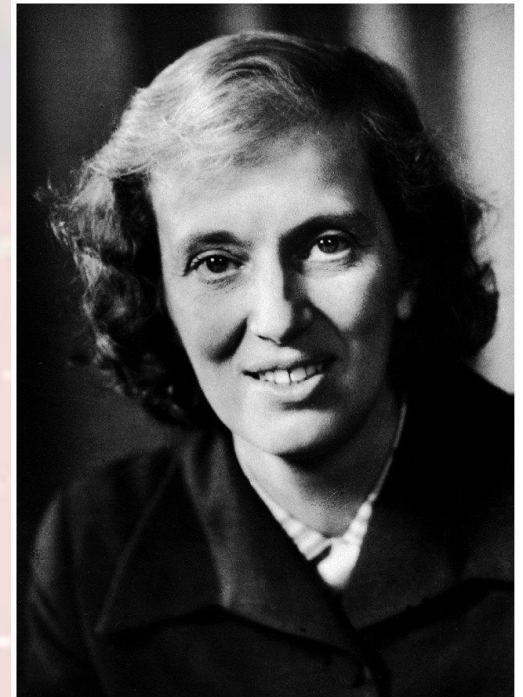


Garrett/Grisham, Biochemistry with a Human Focus
Figure 14.24



Vitamin B12

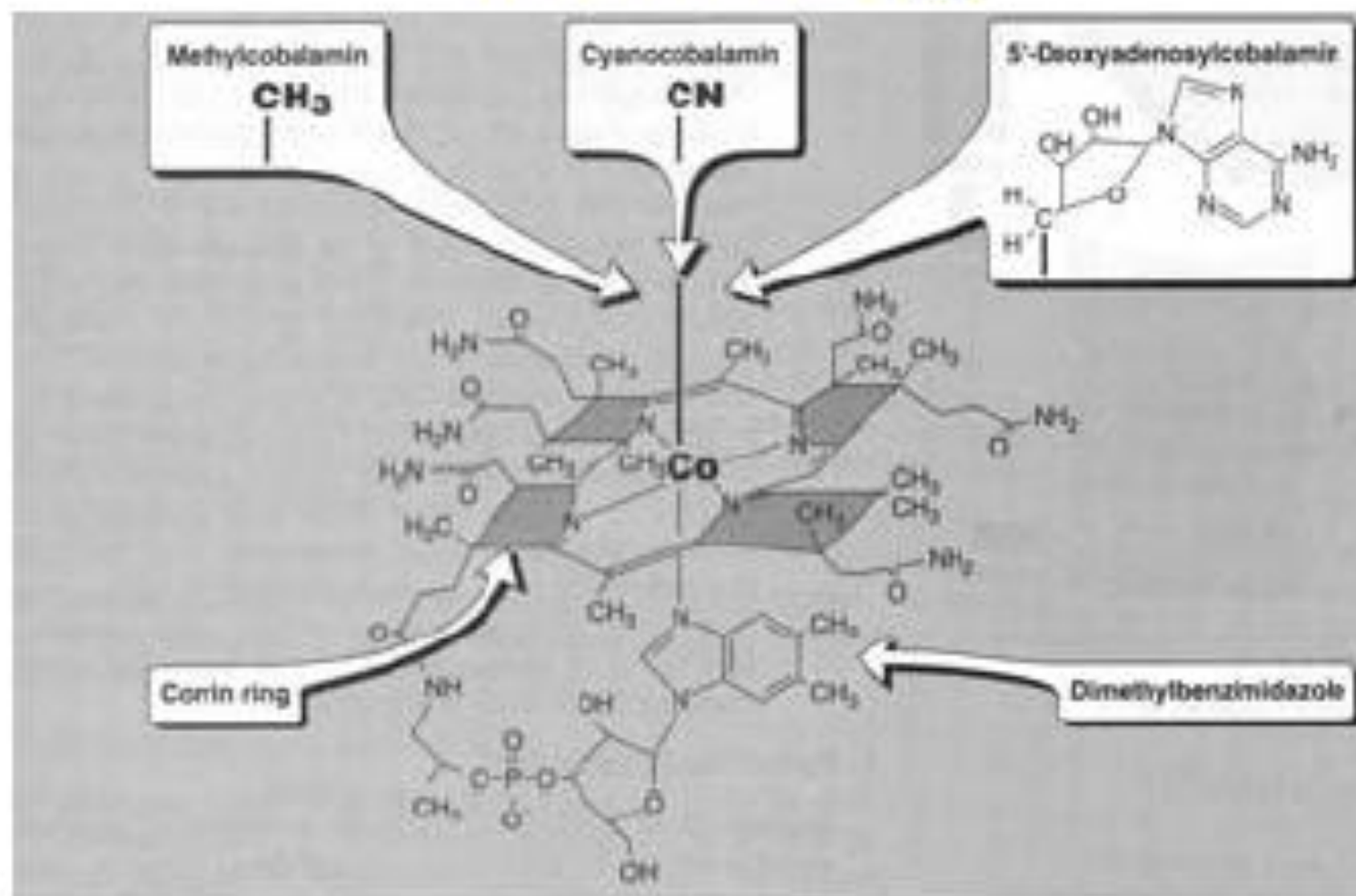
- ❖ Vitamin B12 helps maintain healthy nerve and red blood cells
- ❖ It is found in fish, meat, poultry, eggs, milk, and milk products
- ❖ Vegans are in danger of deficiency
- ❖ Other foods such as breakfast cereals are commonly supplemented with B12
- ❖ Vitamin B12 deficiency results in reduced levels of hemoglobin and nervous system impairment that may be irreversible
- ❖ Folic acid can correct the anemia from B12 deficiency, but it cannot correct the nerve damage!
- ❖ Take both together...



Dorothy Crowfoot Hodgkin
1910–1994

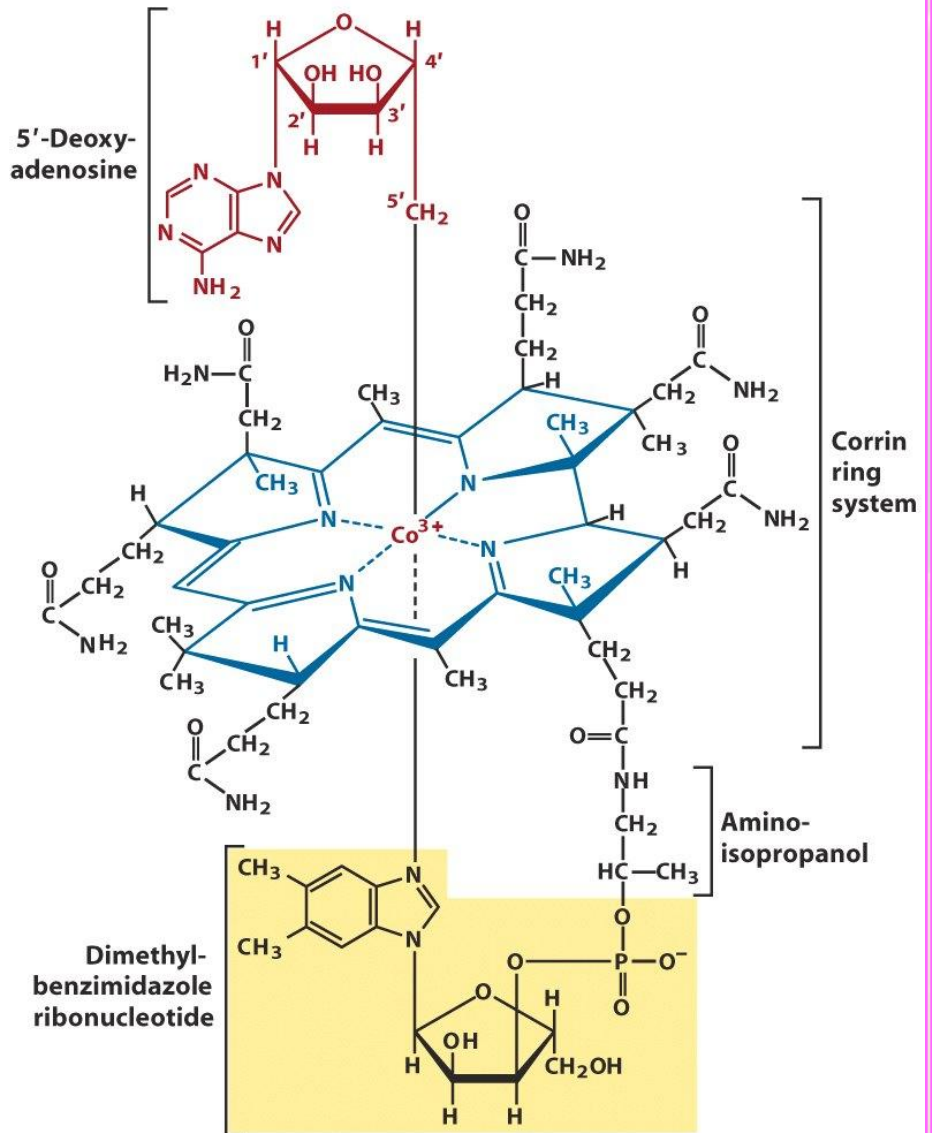
**Determined 3-D
structure in 1956**

Folate's partner is the Freakiest of all Vitamins: Behold Cobalamin: Vitamin B₁₂



Vitamin B12

- ❖ The first *organometallic* biological molecule
- ❖ Has a cobalt-carbon bond (weak; 110 kJ/mol)
- ❖ Corrin ring
- ❖ With 5'-deoxy-adenosine bound to cobalt, is called coenzyme B12.

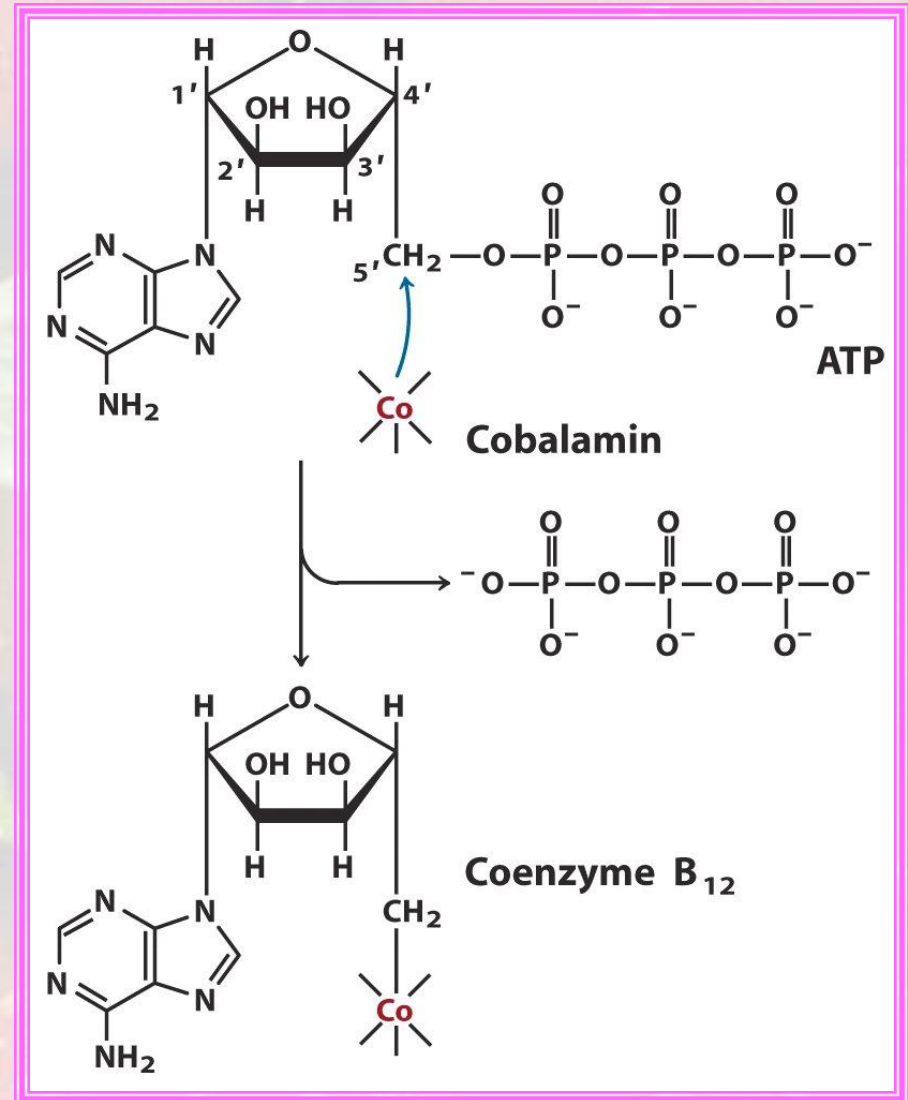
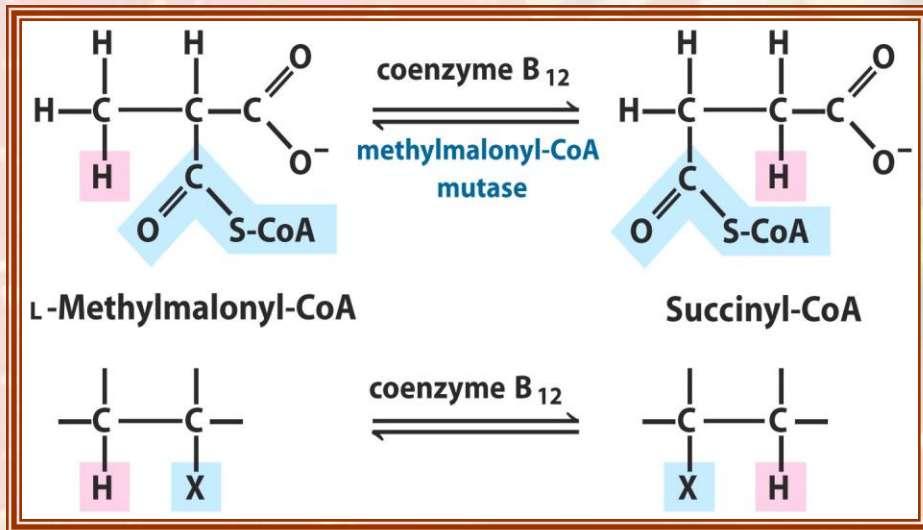


Cobalamin (Vitamin B₁₂)

- ❖ Coenzymes: methylcobalamin, adenosylcobalamin
- ❖ Cobalamin contains a corrin ring system and a cobalt (it is synthesized by only a few microorganisms)
- ❖ Humans obtain cobalamin from foods of animal origin (deficiency leads to pernicious anemia)
- ❖ Coenzymes participate in enzyme-catalyzed molecular rearrangements in which an H atom and a second group on the substrate exchange places

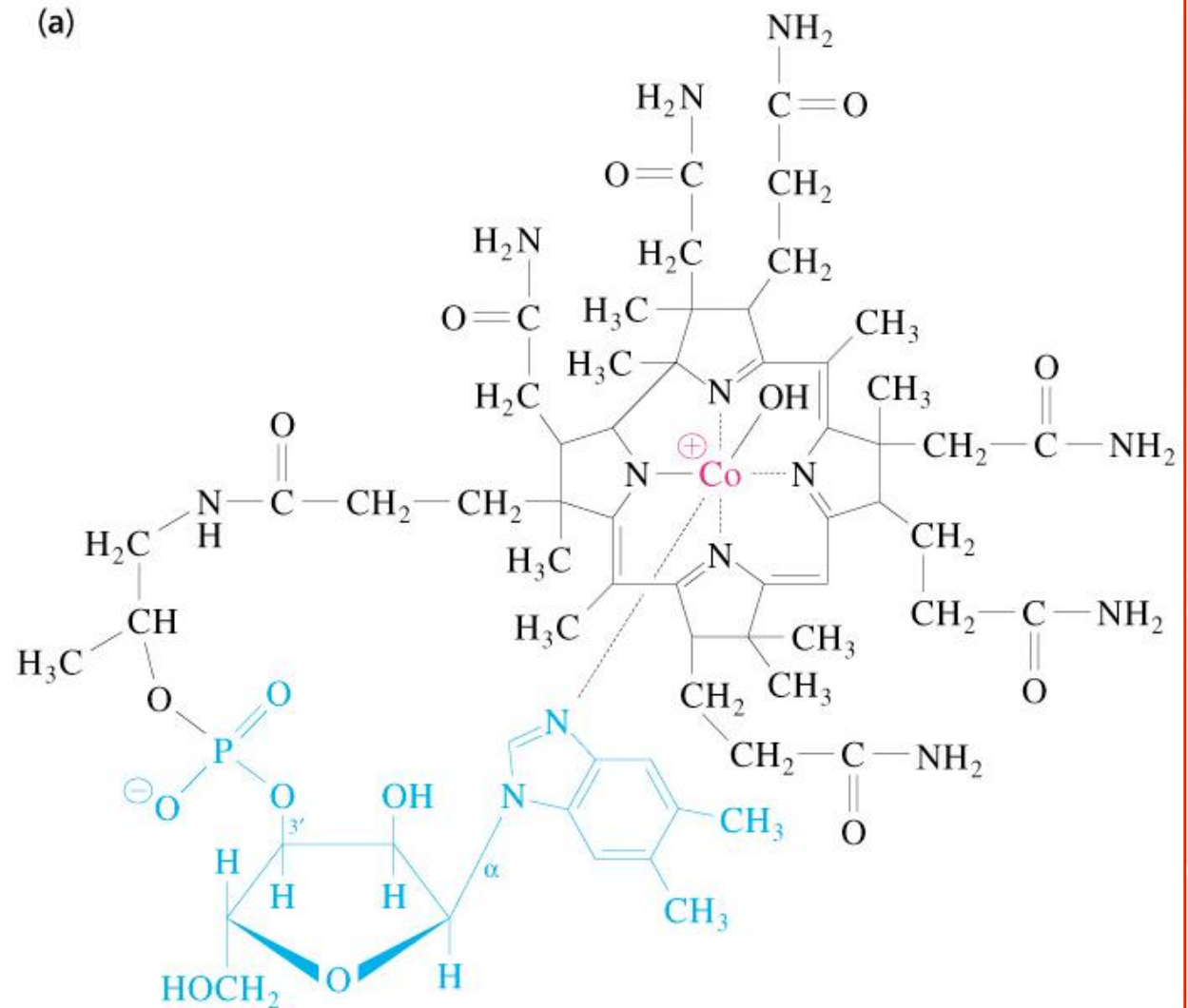
Vitamin B12

- Coenzyme B12 is an important cofactor for alkyl group transfers.
- Groups are transferred as radicals; weak Co-C bond assists with this.



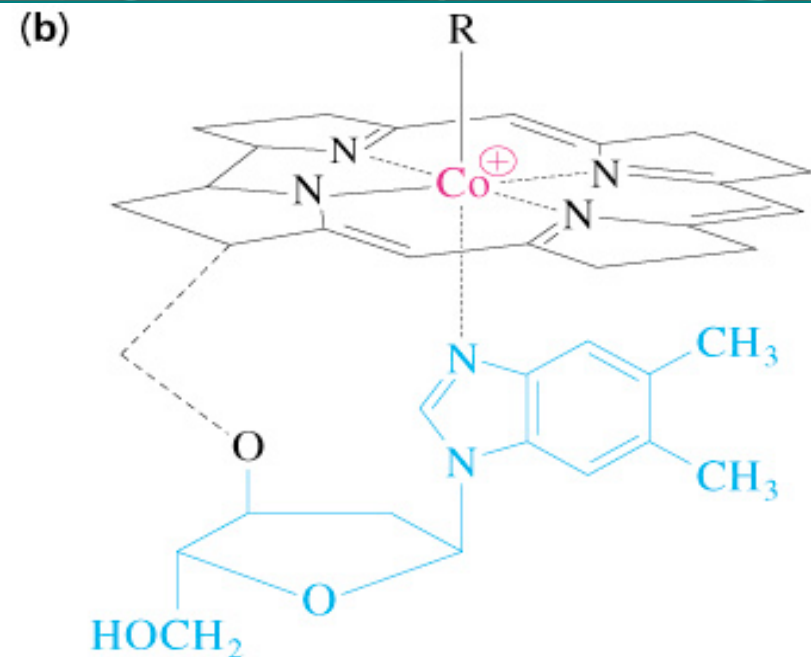
Cobalamin (Vit B₁₂) and its coenzymes

(a) Cobalamin.
Corrin ring
(black), is
not
aromatic

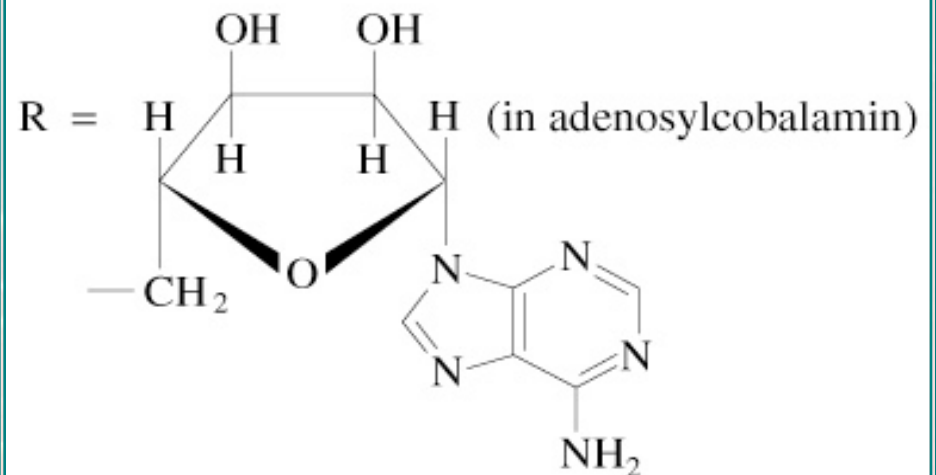


(b) Abbreviated structure of cobalamin coenzymes

(c) Note the 5' deoxy adenosyl attachment



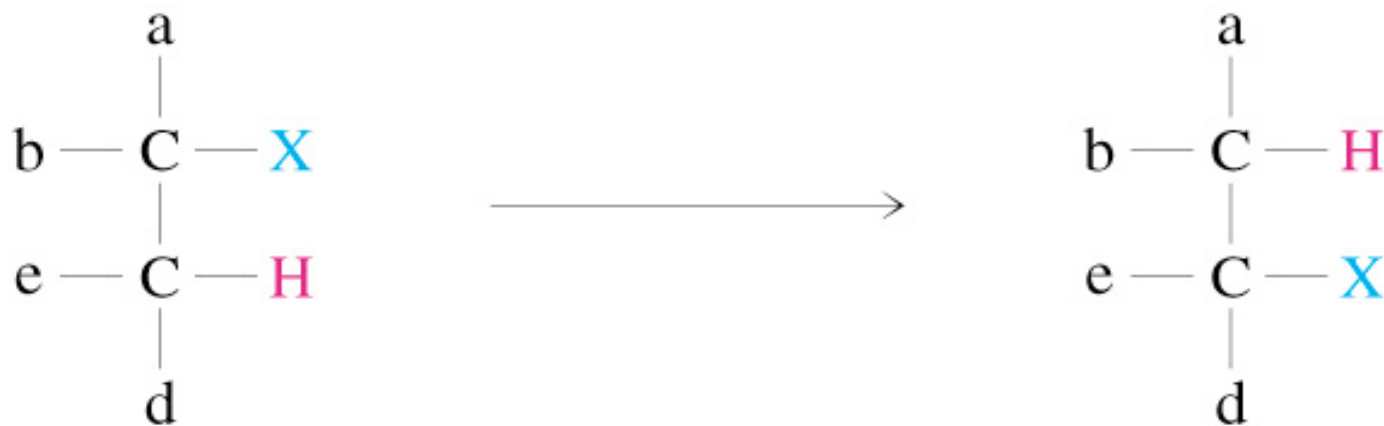
R = —CH₃ (in methylcobalamin)



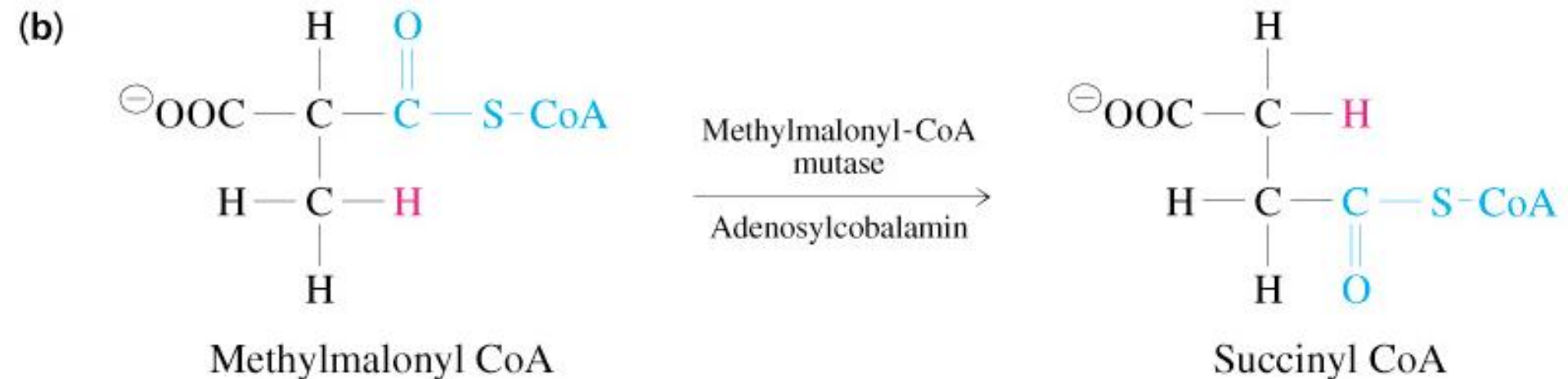
Intramolecular rearrangements catalyzed by adenosylcobalamin enzymes

(a) Rearrangement of an H and substituent X on an adjacent carbon

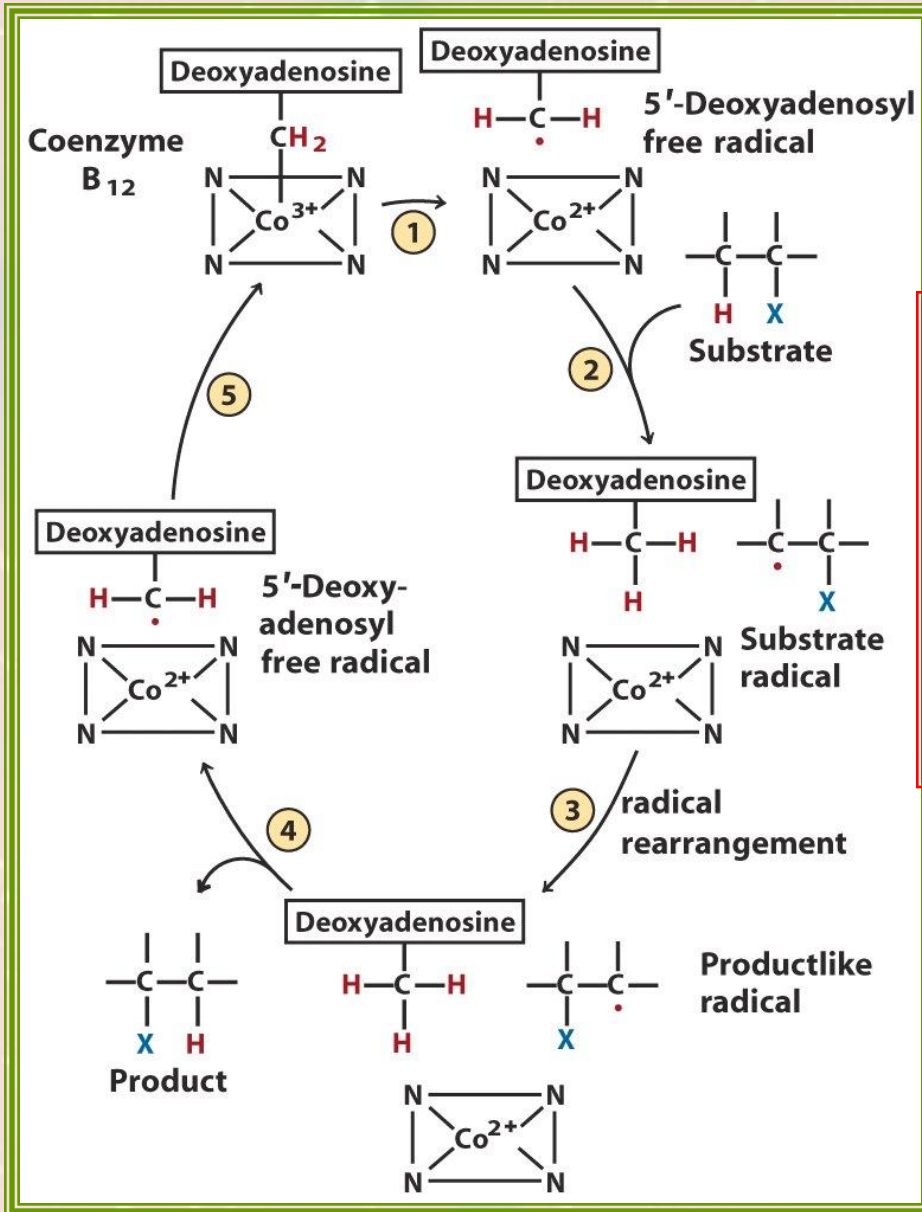
(a)



(b) Rearrangement of methylmalonyl CoA



Vitamin B12



Methylmalonyl-CoA mutase mechanism

