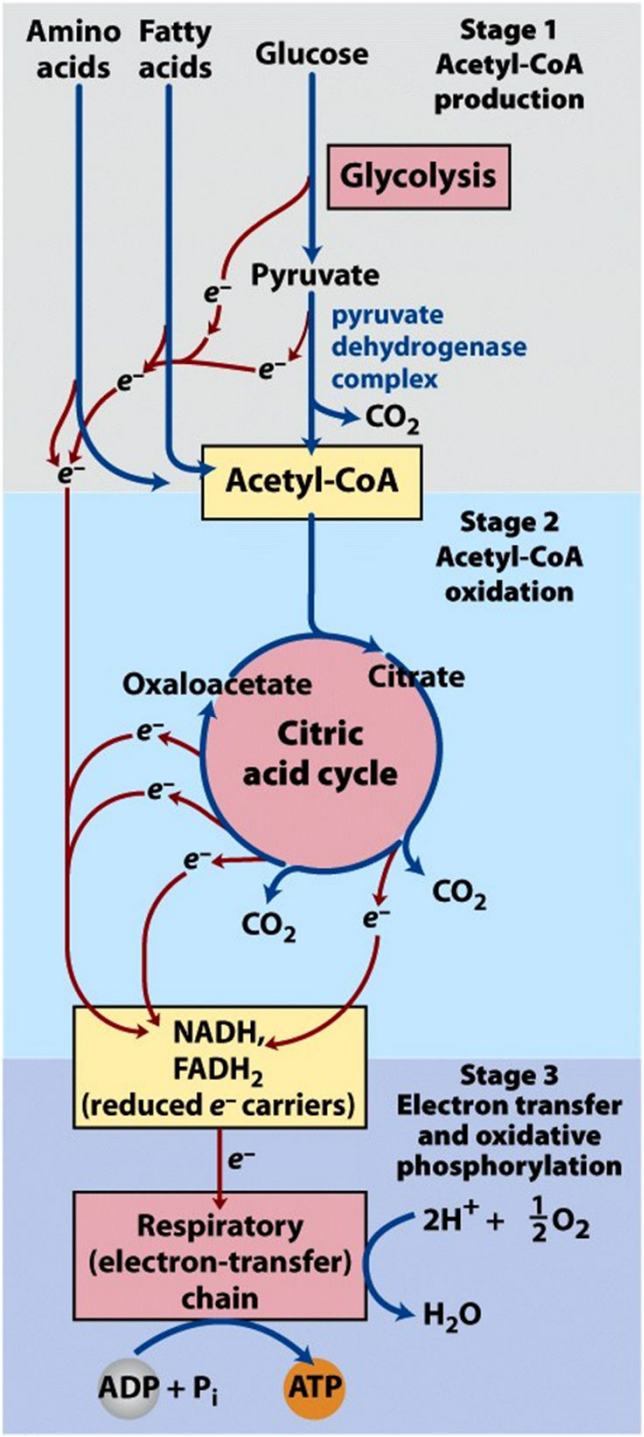
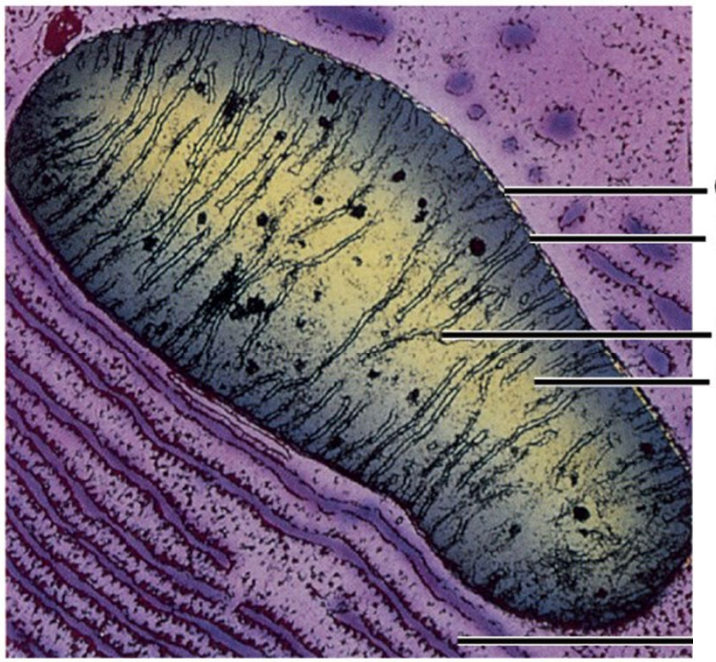
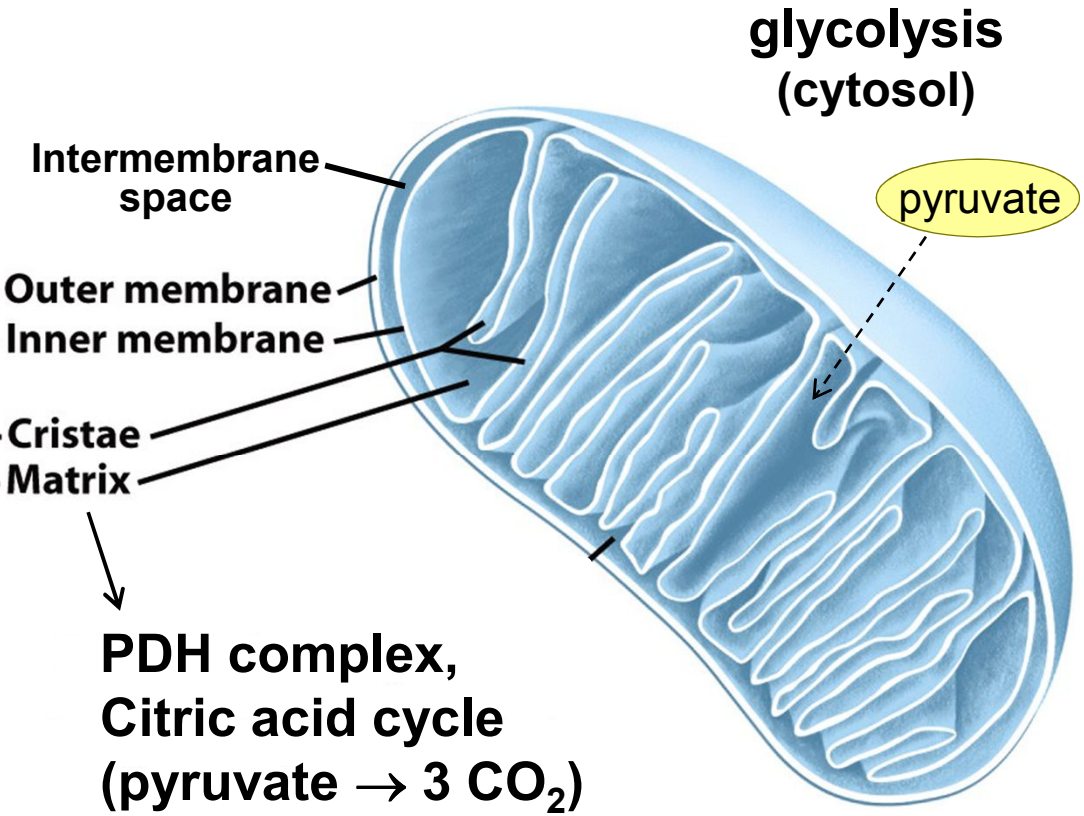
The breakdown of sugars, proteins, and fats converges on a common oxidative pathway



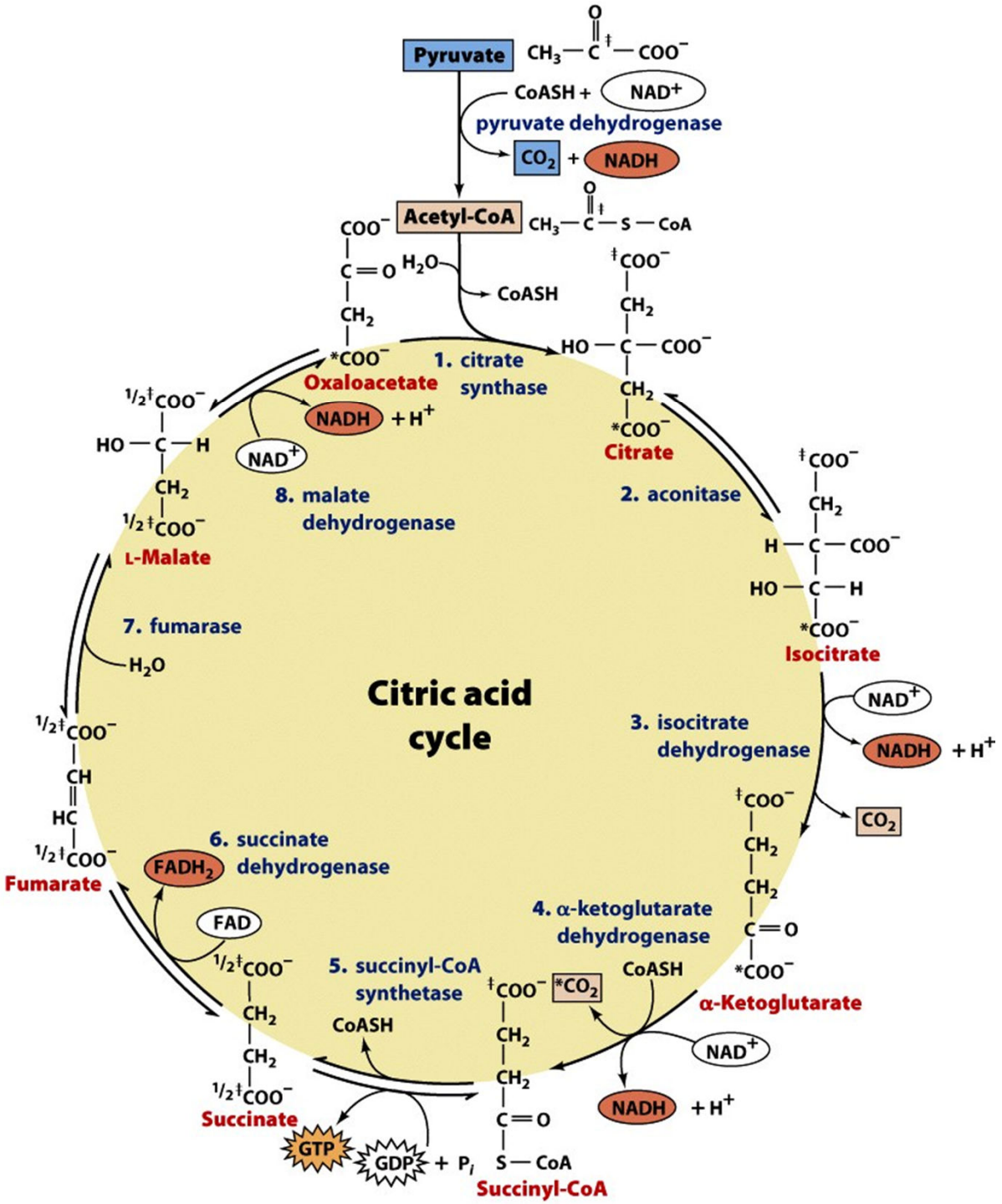
Aerobic metabolism occurs in mitochondria



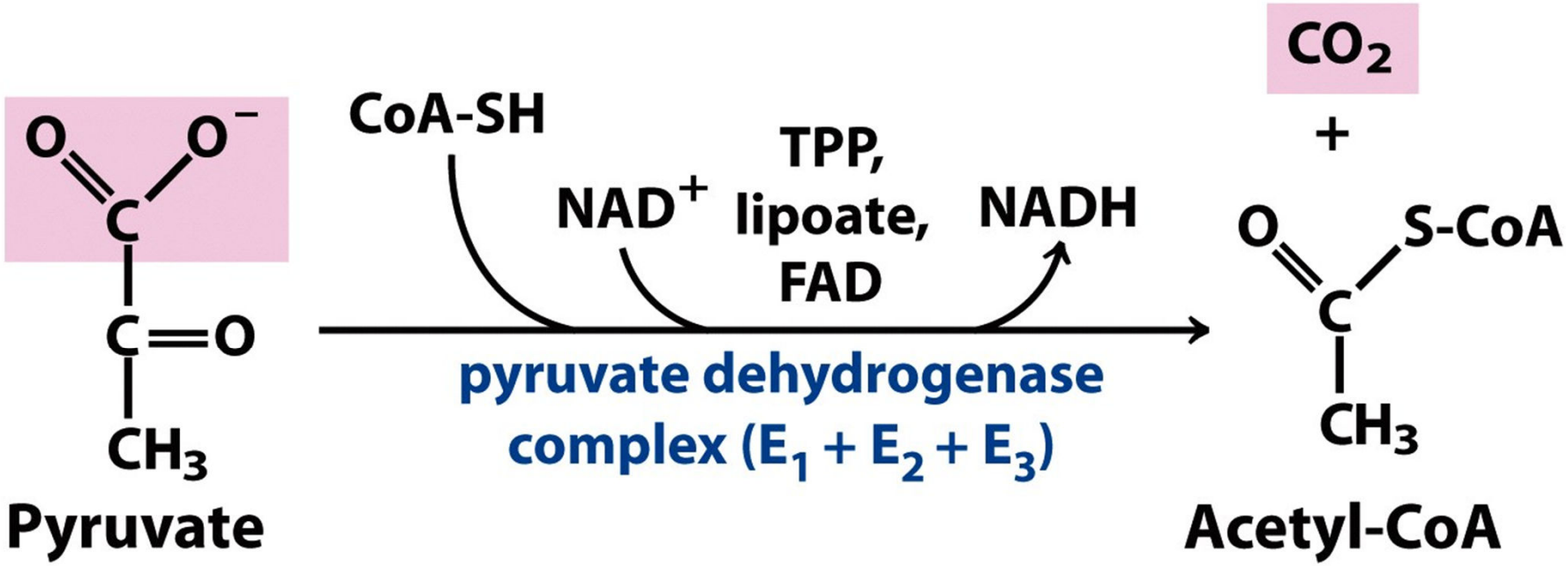


PDH complex,
Citric acid cycle
(pyruvate $\rightarrow$ 3 CO_2)

Oxidation of electron carriers
ATP synthesis
(by protein complexes in the inner mb)


Pyruvate
CoASH +
NAD+
pyruvate dehydrogenase
CO2 +
NADH
Acetyl-CoA
CoASH
1. citrate synthase
Oxaloacetate
Citrate
2. aconitase
Isocitrate
3. isocitrate dehydrogenase
NAD+
NADH + H+
CO2
4. α-ketoglutarate dehydrogenase
α-Ketoglutarate
5. succinyl-CoA synthetase
GTP
GDP + Pi
Succinyl-CoA
6. succinate dehydrogenase
FADH2
FAD
Fumarate
7. fumarase
H2O
8. malate dehydrogenase
L-Malate
Citric acid cycle

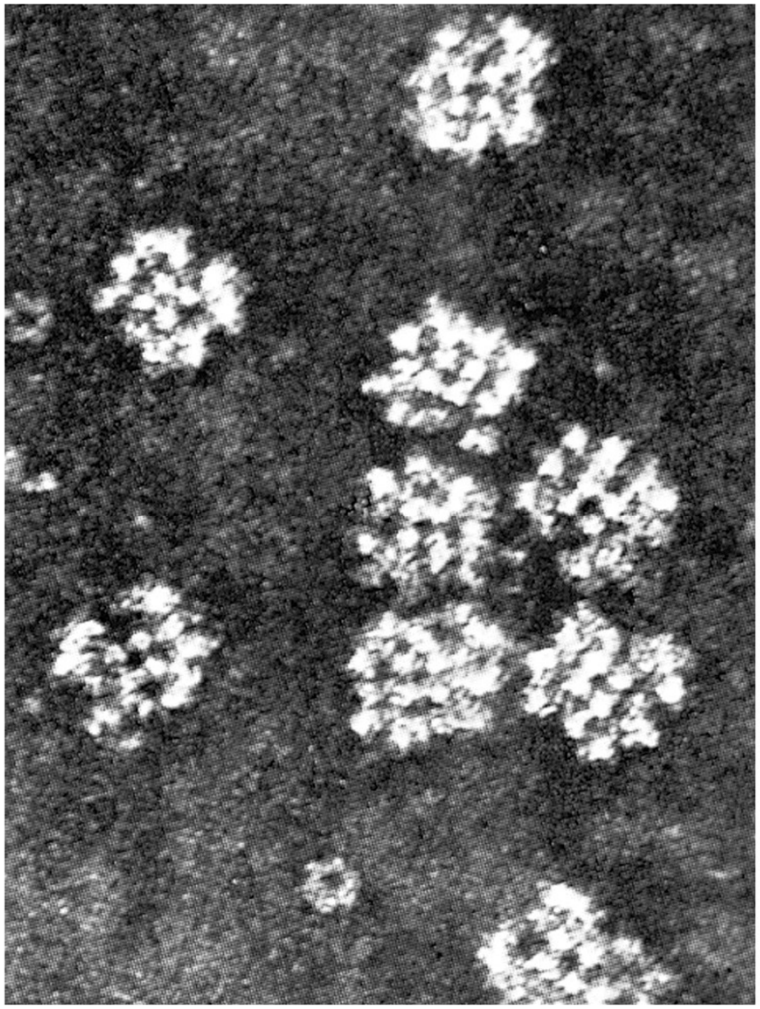
Pyruvate is oxidatively decarboxylated to acetyl-CoA in an irreversible reaction



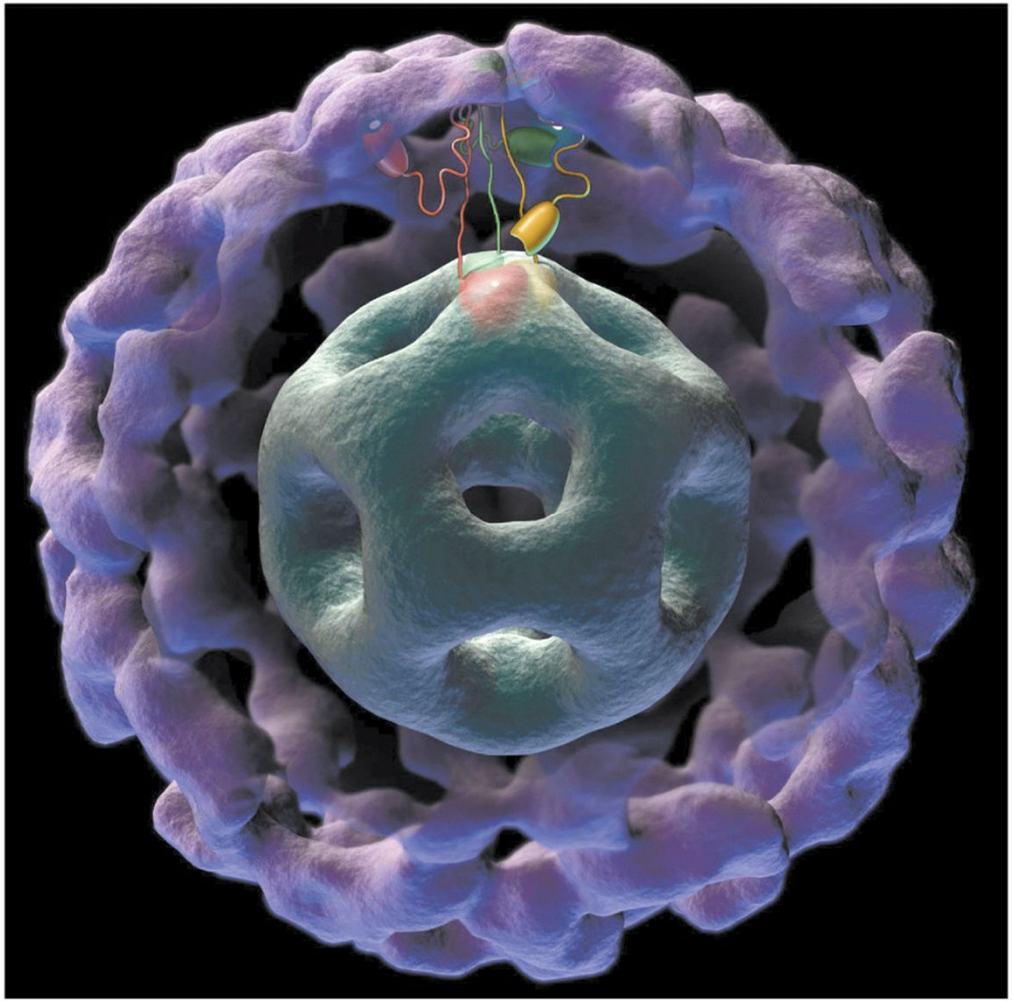
	Oxidation:	exergonic
	Decarboxylation:	exergonic
+	Thioester formation:	endergonic
	Net reaction:	exergonic

$\Delta G'^{\circ} = -33.4$ kJ/mol

Pyruvate DH complex is a huge multi-enzyme structure, with dozens of subunits



Courtesy of Lester Reed, University of Texas at Austin

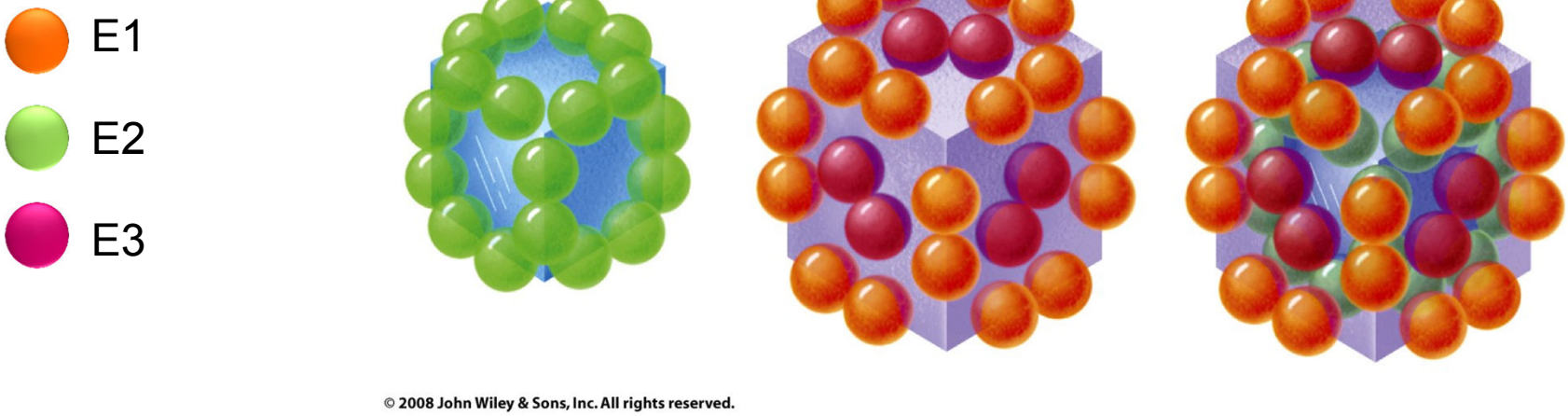


Courtesy of Jacqueline Milne, National Institutes of Health, Bethesda, MD

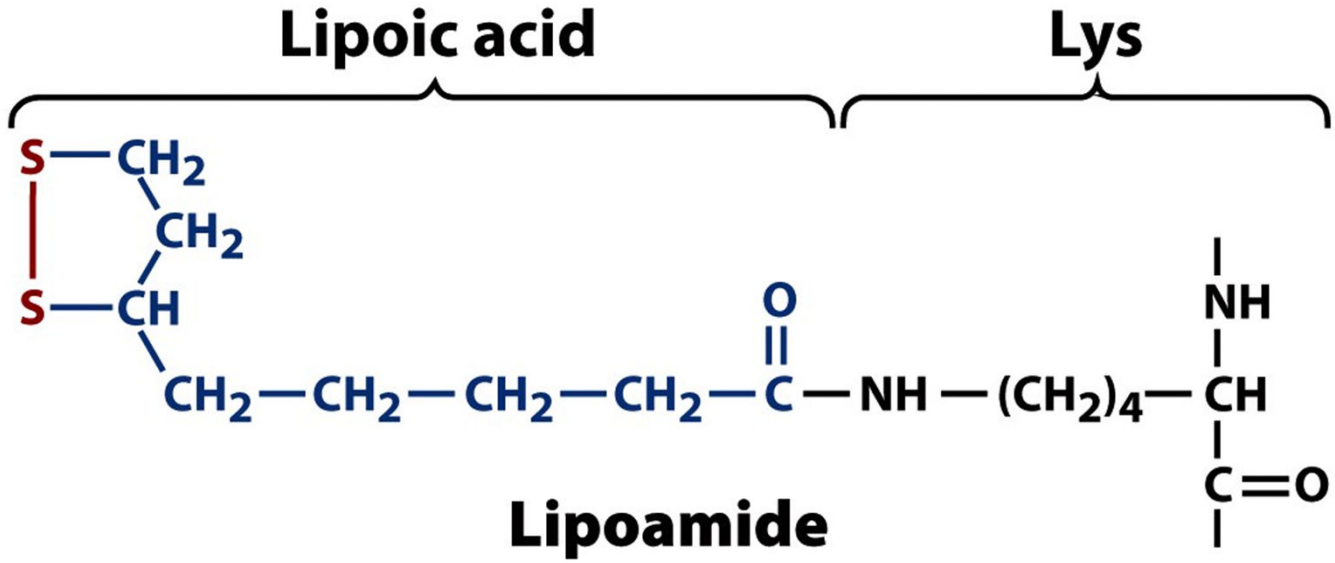
PDH complex is composed of three major enzymes

Enzyme	Name	Cofactors	# in *E. coli*	# in mammals
E1	Pyruvate DH	TPP	24	~45 $\alpha_2\beta_2$ tetramers
E2	Dihydrolipoyl transacetylase	Lipoic acid, Coenzyme A	24	60
E3	Dihydrolipoyl DH	FAD, NAD	12	~9 homodimers

Arrangement in *E. coli*:



Lipoic acid is covalently bound to a lysine of E2 to form lipoamide



PDH complex carries out the oxidative decarboxylation of pyruvate in 5 steps

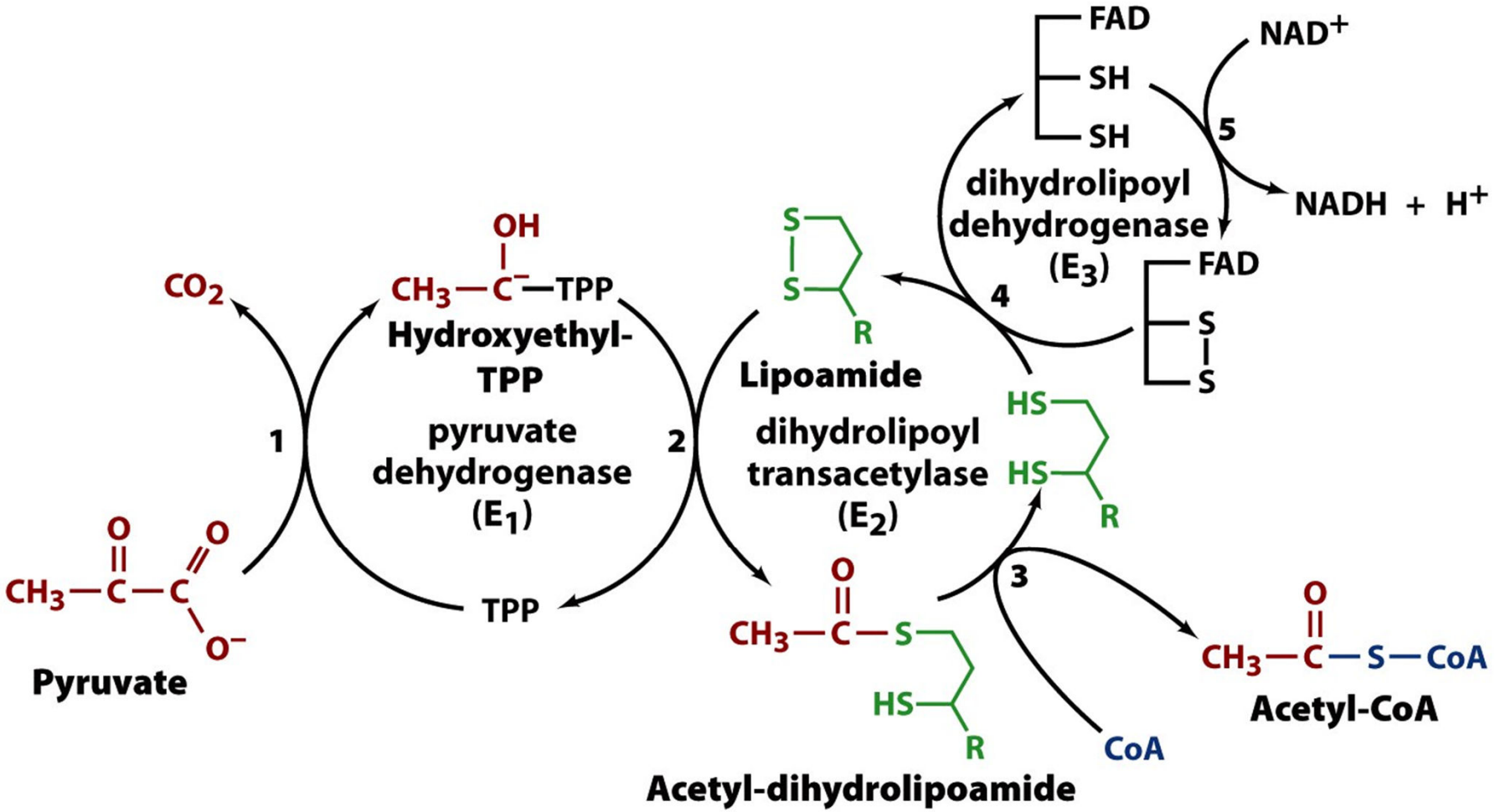
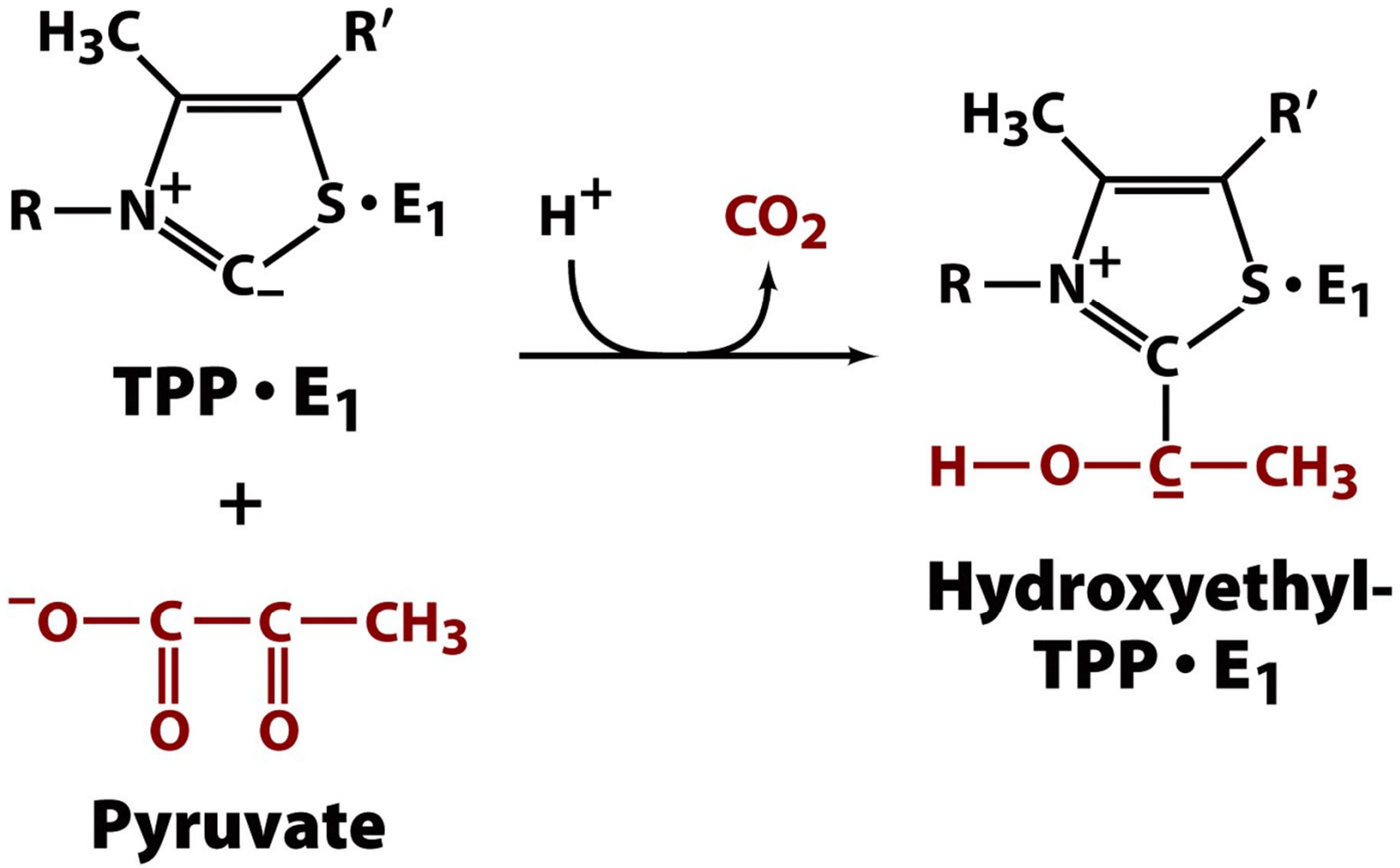


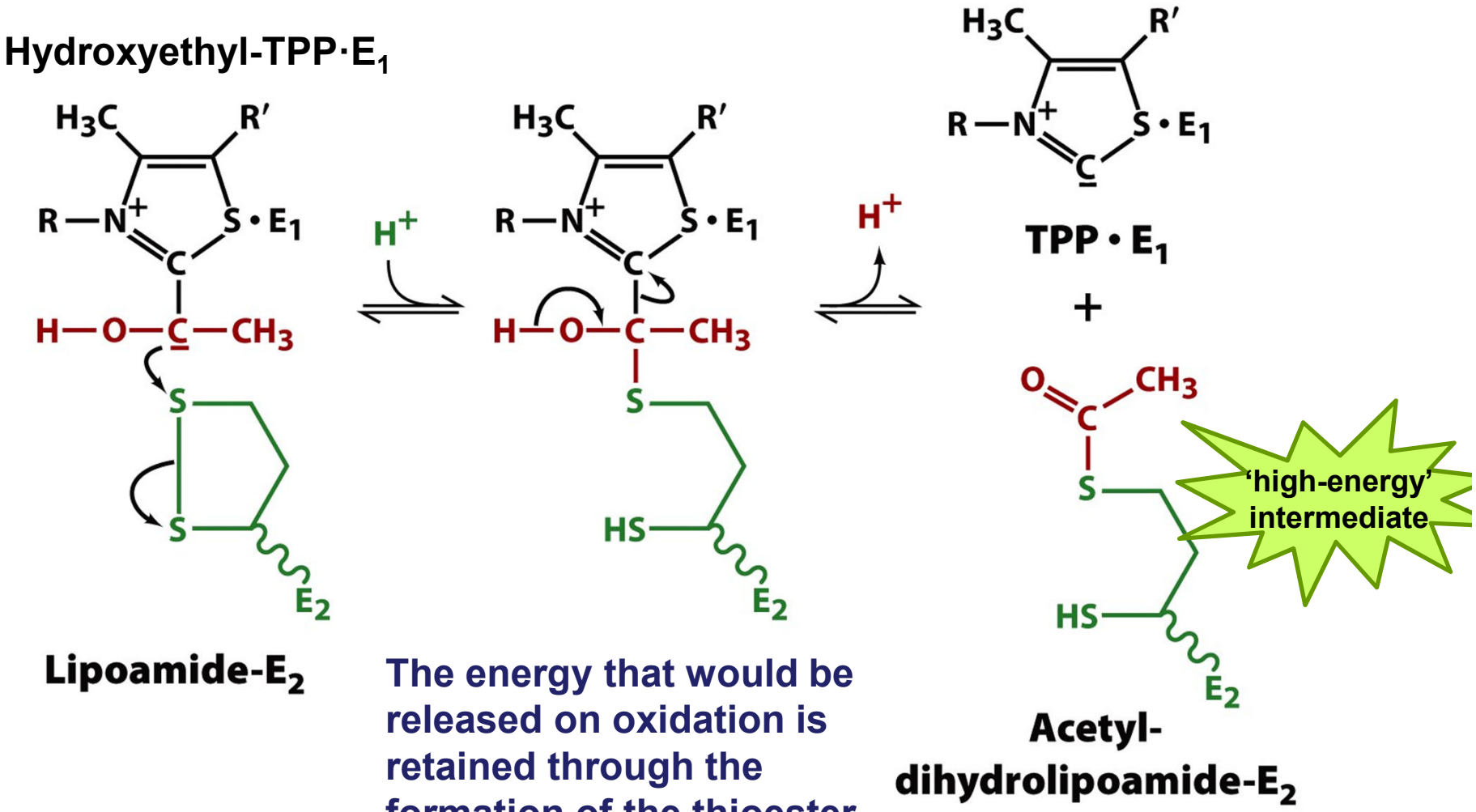
Table 17-1 The Coenzymes and Prosthetic Groups of Pyruvate Dehydrogenase

Cofactor	Location	Function
Thiamine pyrophosphate (TPP)	Bound to E_1	Decarboxylates pyruvate yielding a hydroxyethyl-TPP carbanion
Lipoic acid	Covalently linked to a Lys on E_2 (lipoamide)	Accepts the hydroxyethyl carbanion from TPP as an acetyl group
Coenzyme A (CoA)	Substrate for E_2	Accepts the acetyl group from lipoamide
Flavin adenine dinucleotide (FAD)	Bound to E_3	Reduced by lipoamide
Nicotinamide adenine dinucleotide (NAD^+)	Substrate for E_3	Reduced by $FADH_2$

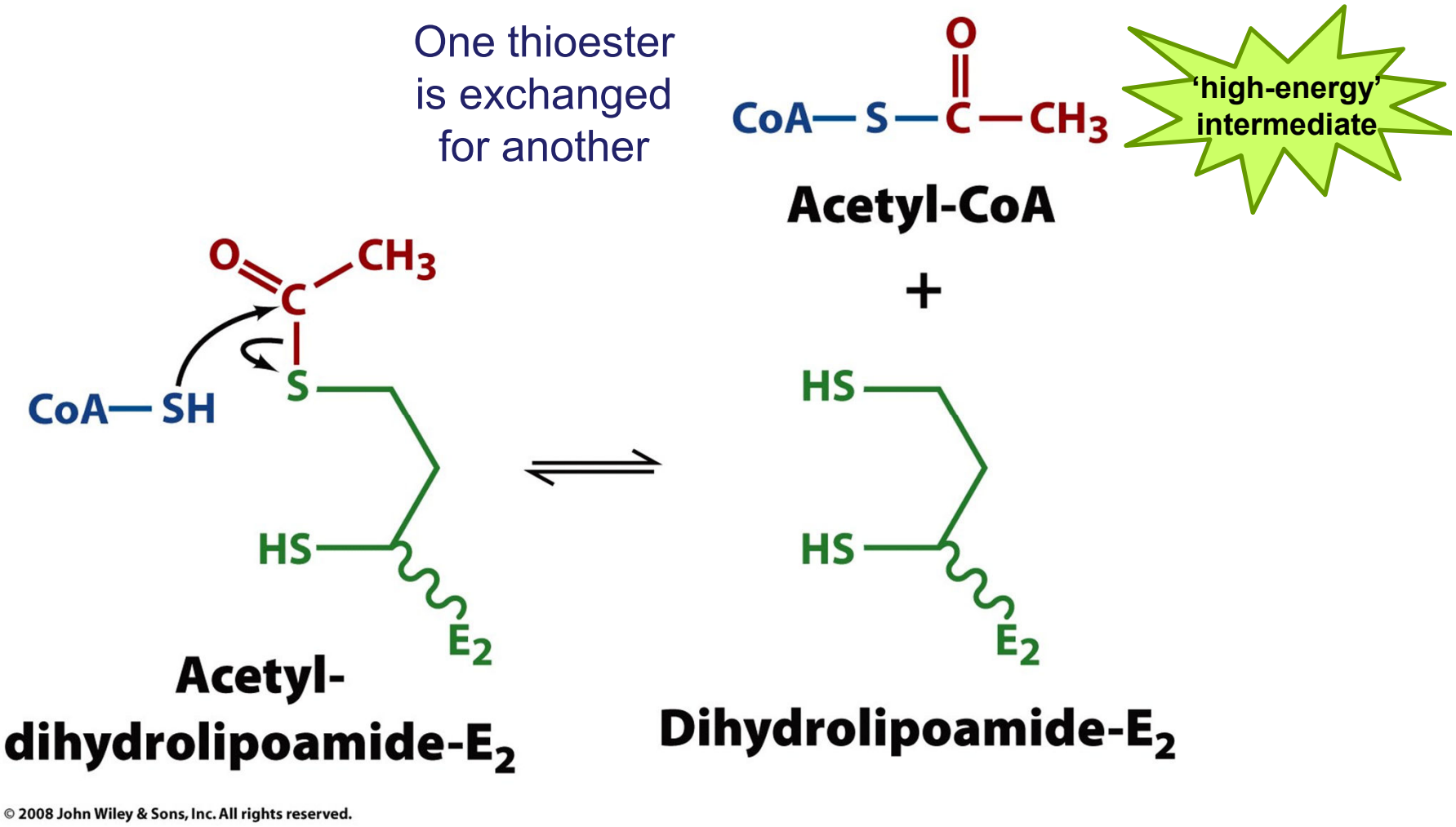
Reaction 1: pyurvate is decarboxylated with the help of TPP (in the E1 active site)



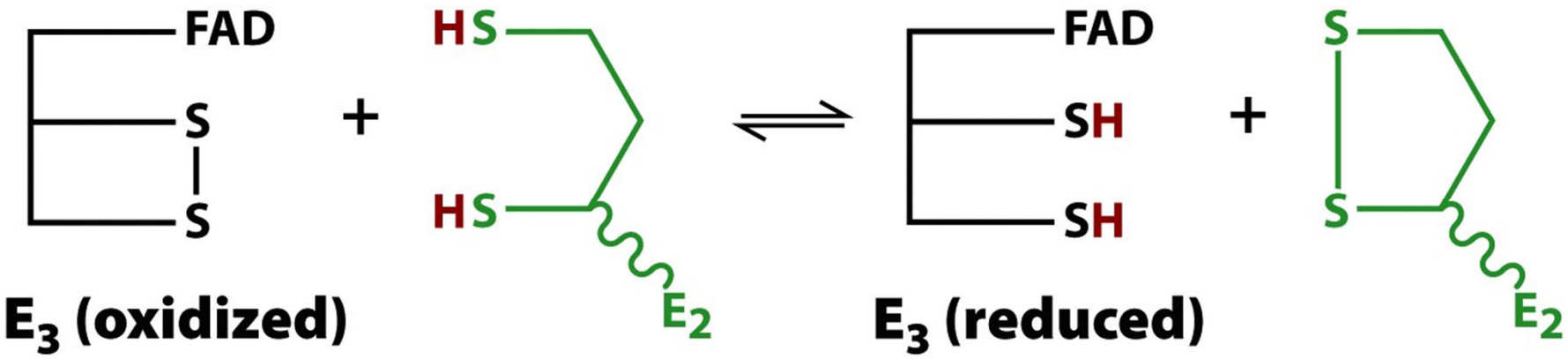
Reaction 2: The carbons are transferred to lipoamide in a redox rxn (in E1's active site)



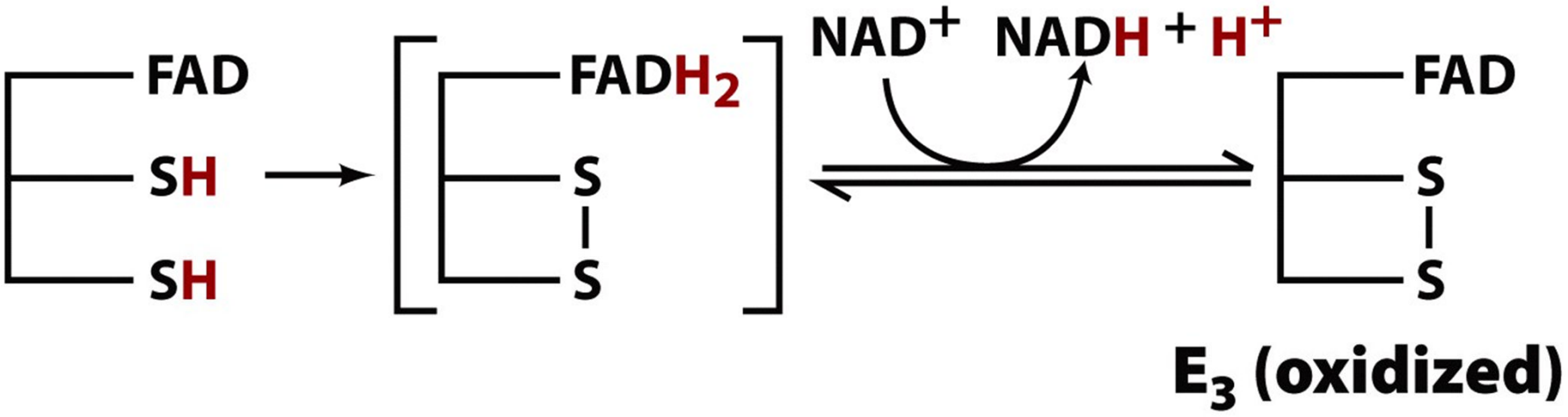
Reaction 3: The acetyl is transferred from dihydrolipoamide to CoA (in E2's active site)



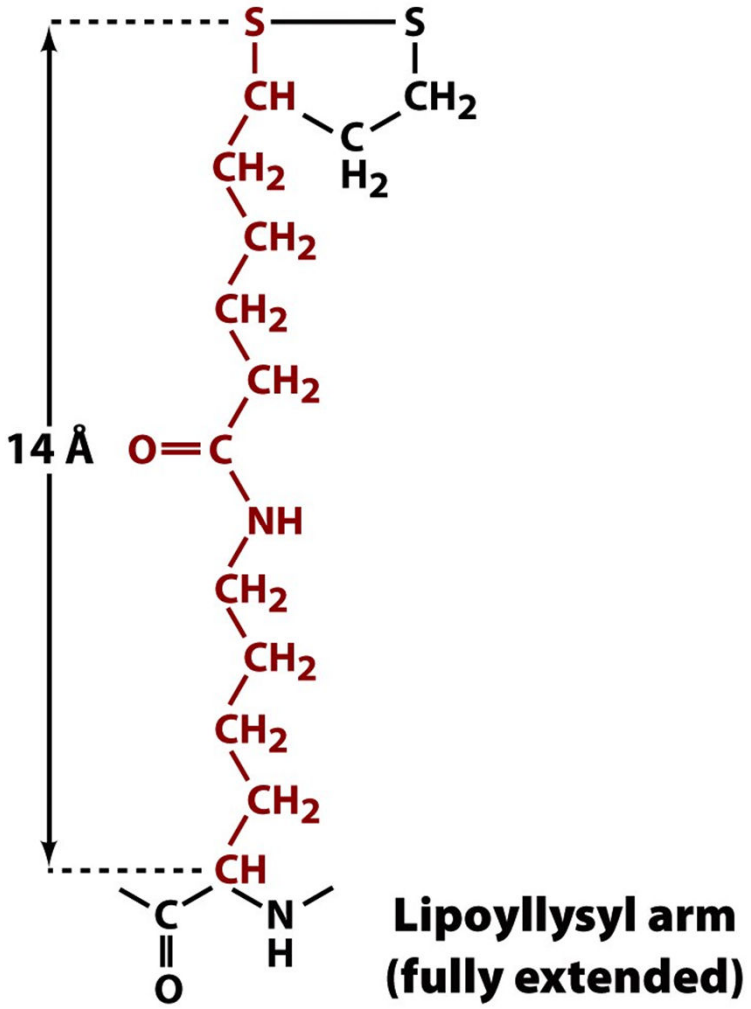
Reaction 4: Dihydrolipoamide is oxidized to lipoamide (in the active site of E3)

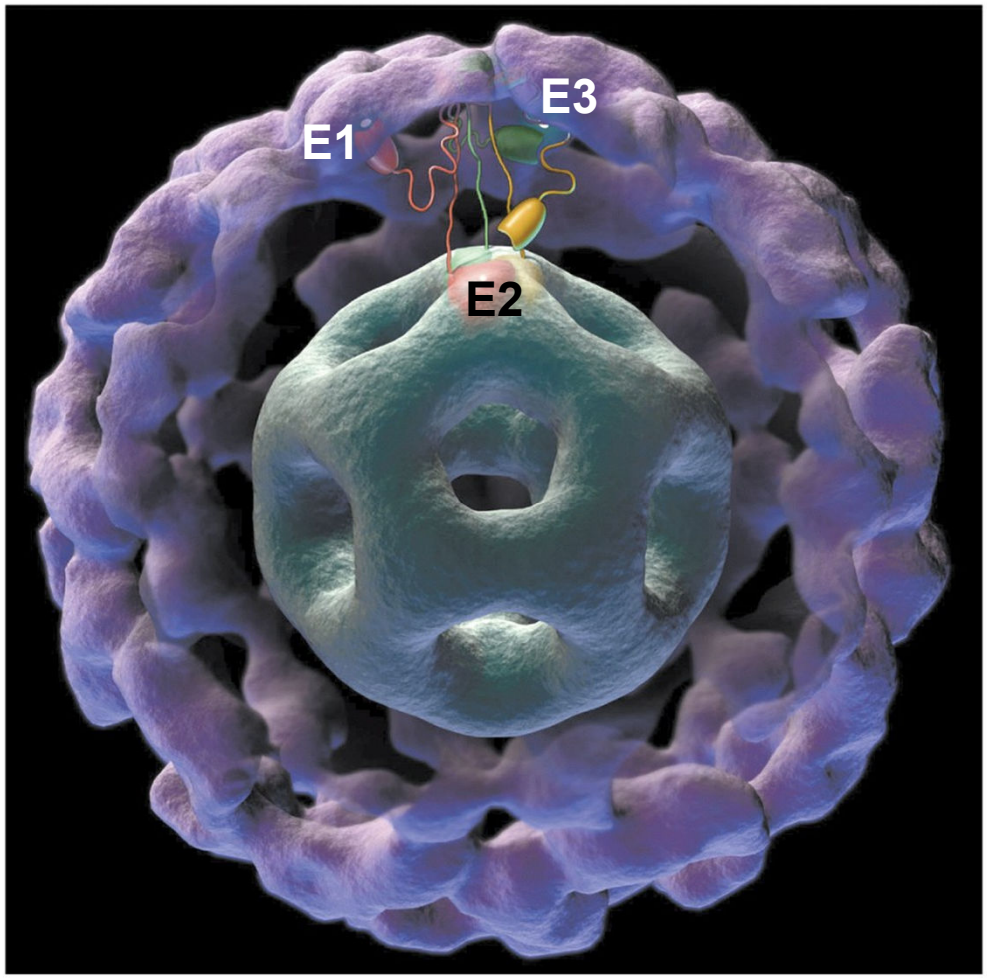


Reaction 5: The thiols of E3 are oxidized and NAD is reduced (in E3's active site)



The length and flexibility of E2's lipoyllysine allows linking of reactions of E1, E2, & E3





Courtesy of Jacqueline Milne, National Institutes of Health, Bethesda, MD