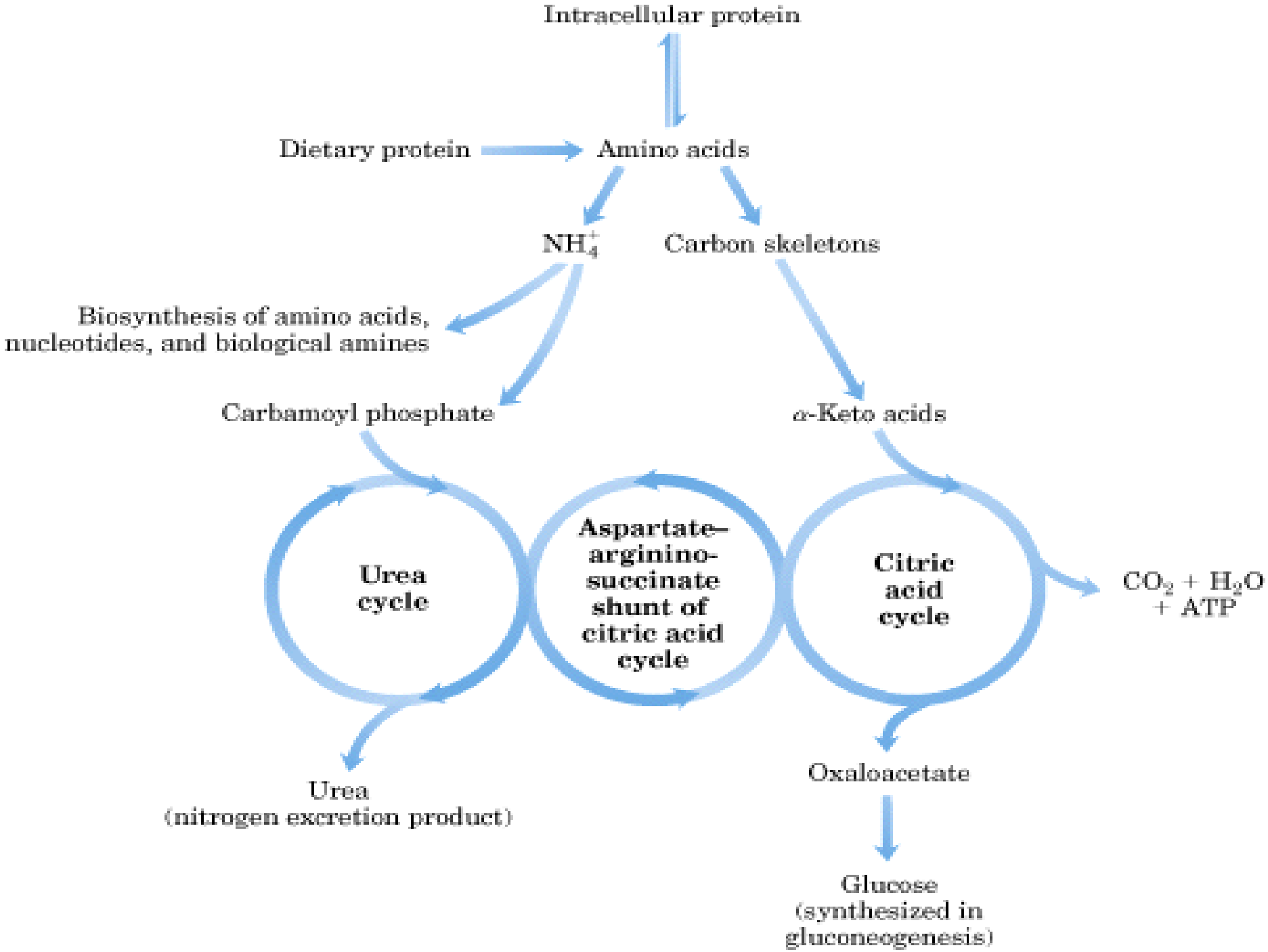
protein Metabolism

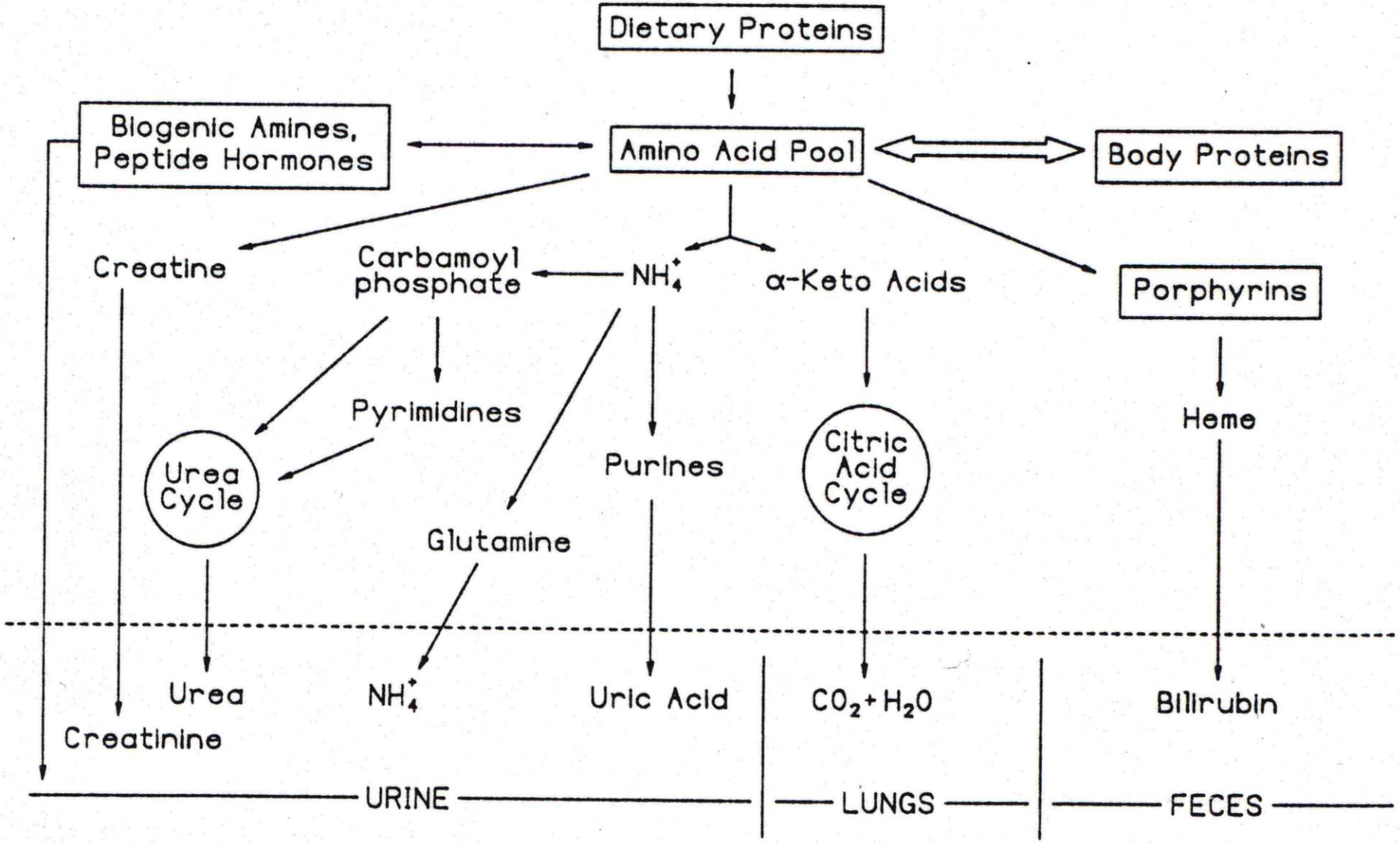
&&

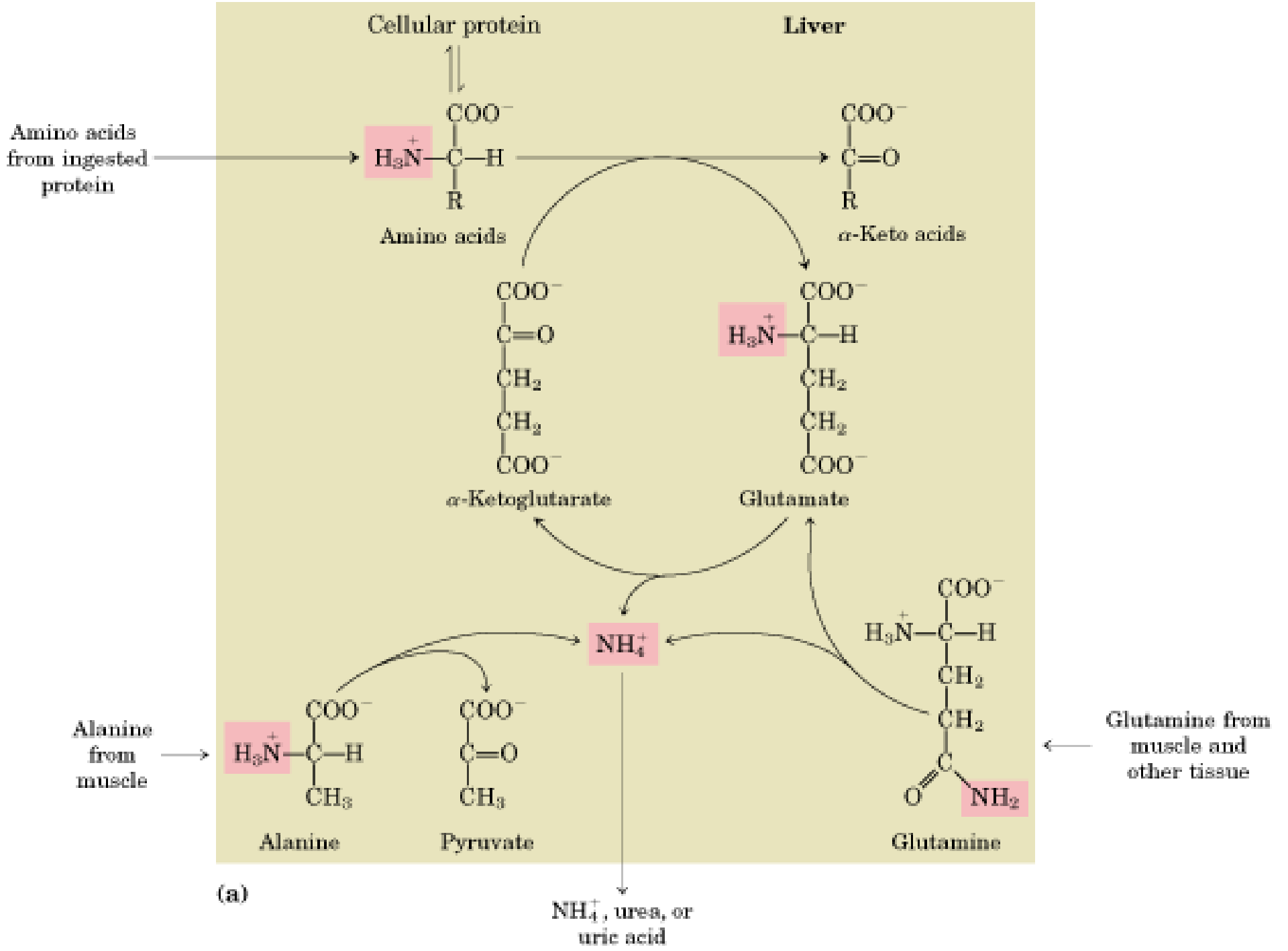
Urea Production

Dr.Sulieman Al-Khalil

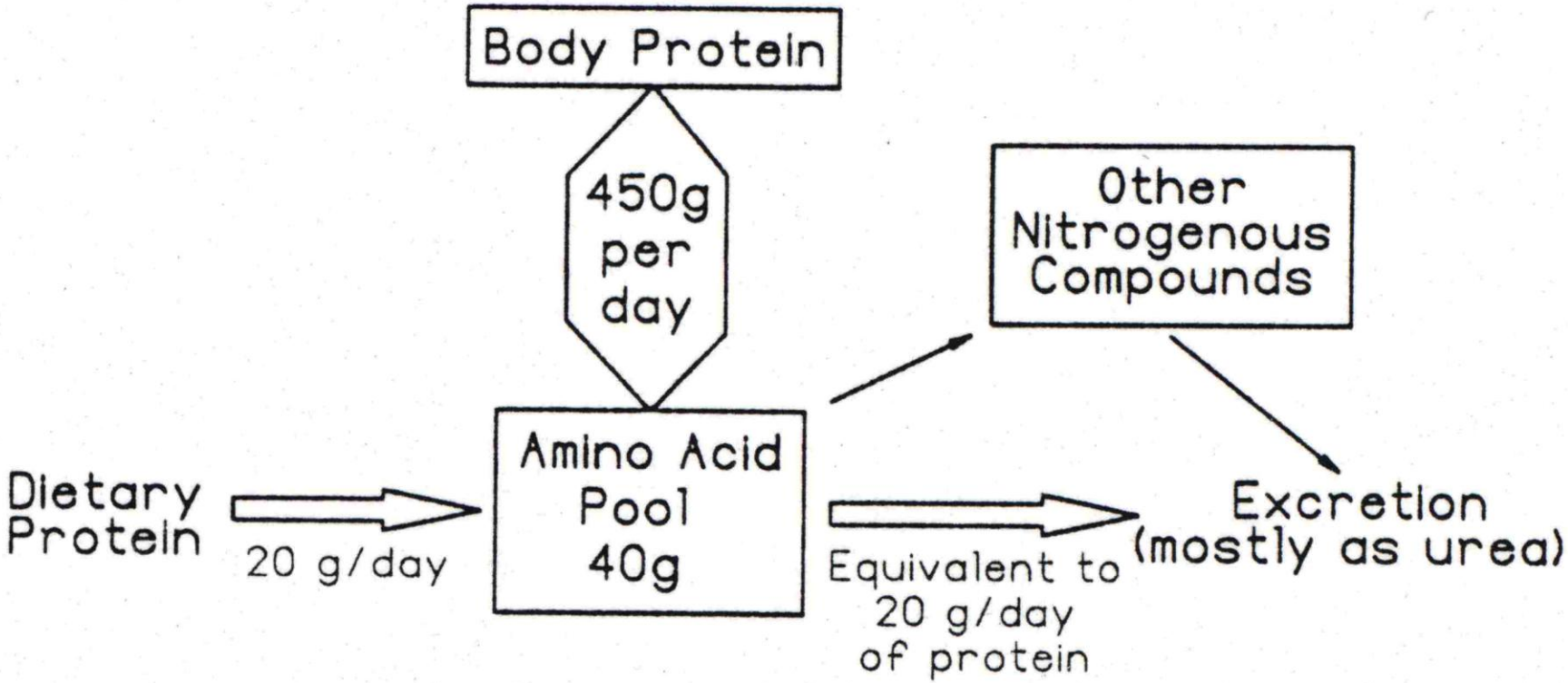

Intracellular protein
Dietary protein
Amino acids
NH_4^+
Carbon skeletons
Biosynthesis of amino acids, nucleotides, and biological amines
Carbamoyl phosphate
α-Keto acids
Urea cycle
Aspartate–arginino-succinate shunt of citric acid cycle
Citric acid cycle
$CO_2 + H_2O$ + ATP
Urea (nitrogen excretion product)
Oxaloacetate
Glucose (synthesized in gluconeogenesis)

Overview of nitrogen metabolism

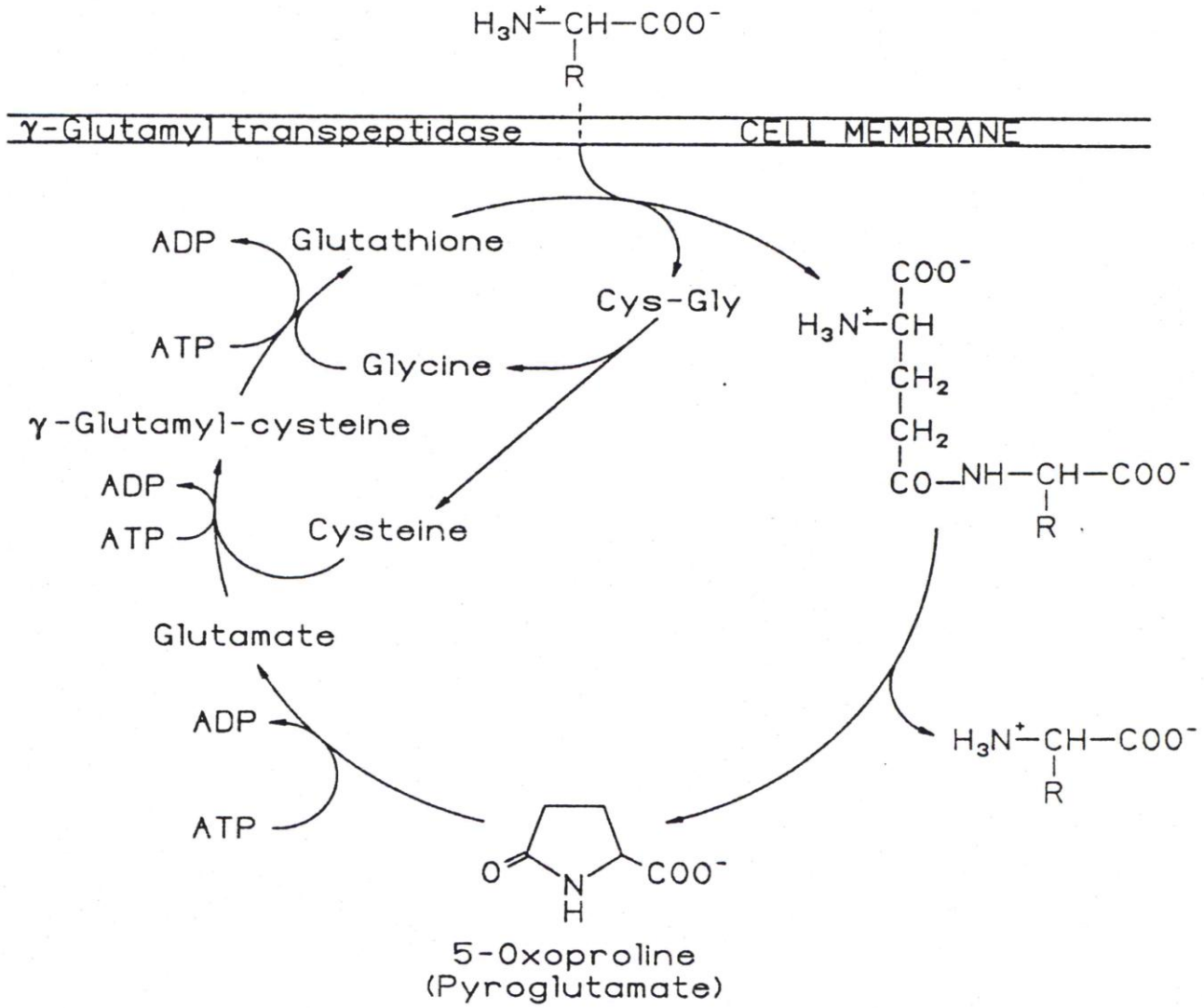



Cellular protein
Liver
Amino acids from ingested protein
Amino acids
α-Keto acids
α-Ketoglutarate
Glutamate
NH4+
Alanine from muscle
Alanine
Pyruvate
Glutamine
Glutamine from muscle and other tissue
(a)
NH4+, urea, or uric acid

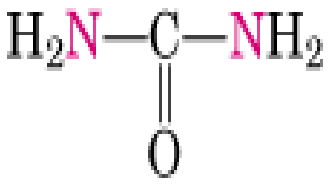
Turnover of the amino acid pool under steady state conditions



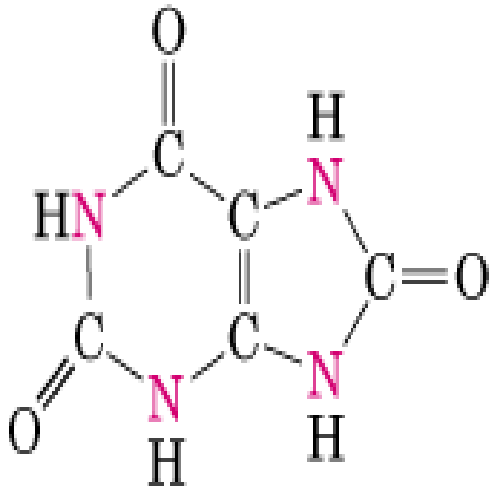
Amino acid transport across the cell membrane (Meister cycle)



Ammonia (as ammonium ion)



Urea



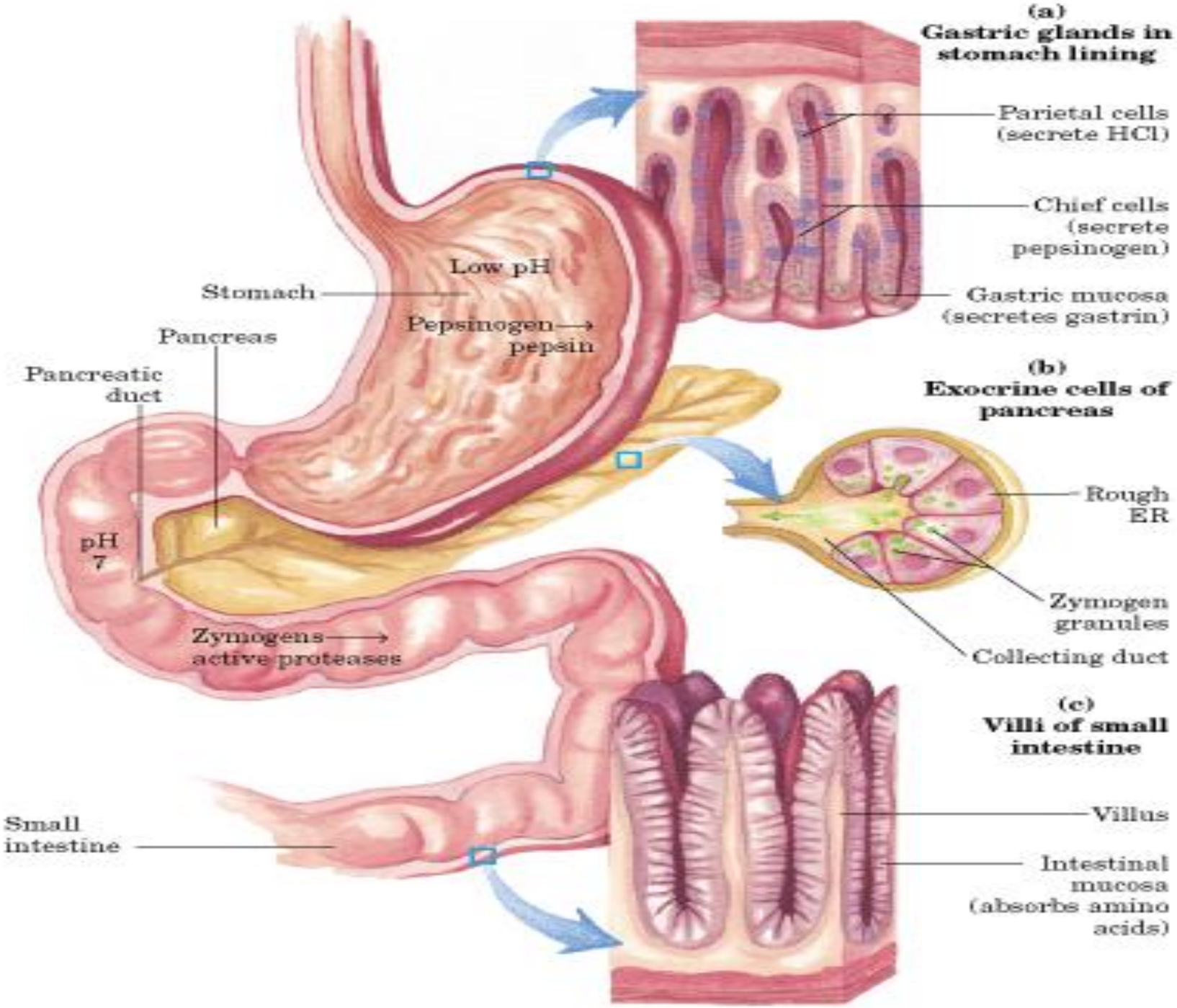
Uric acid

Ammonotelic animals: most aquatic vertebrates, such as bony fishes and the larvae of amphibia

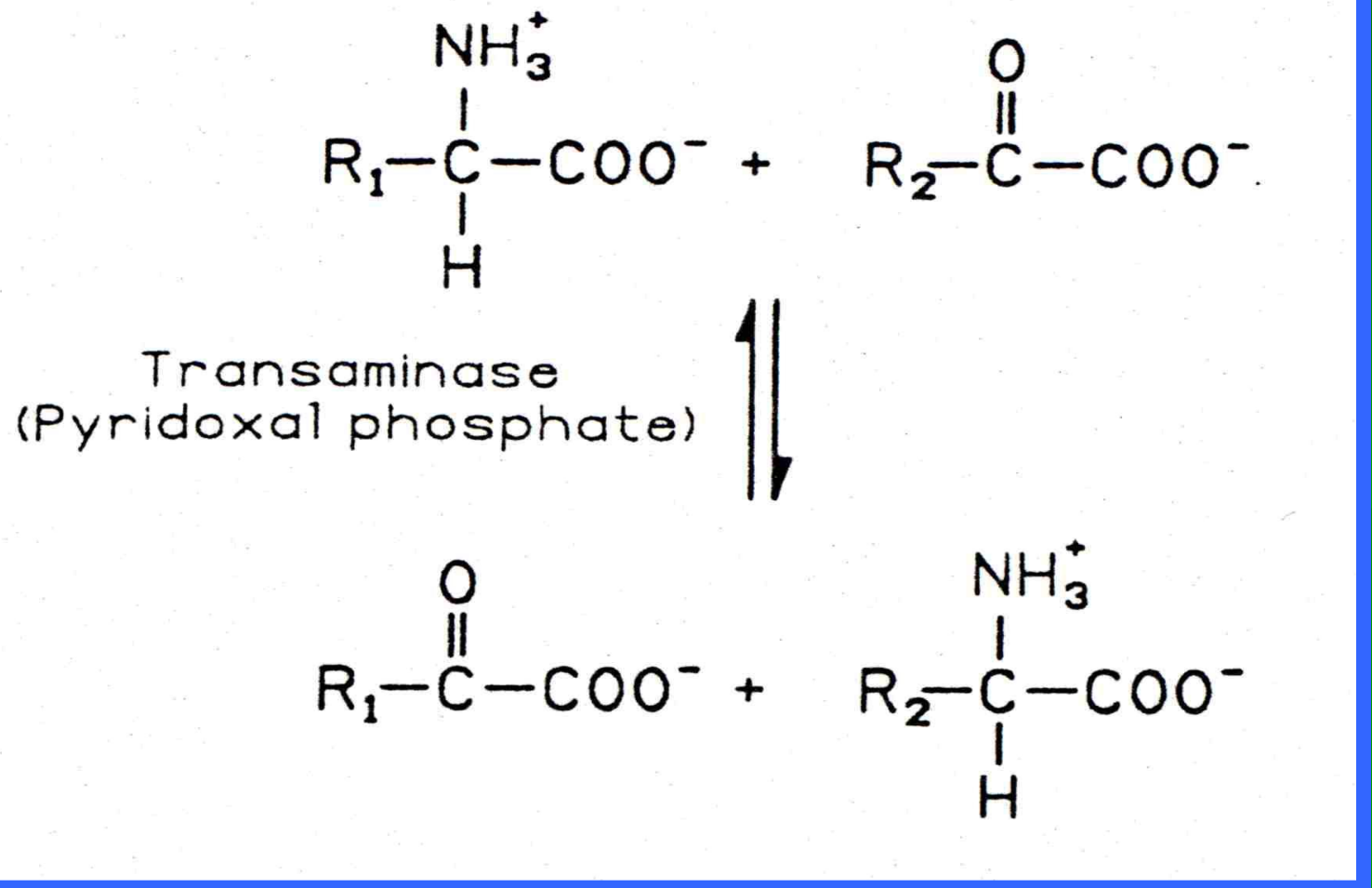
Ureotelic animals: many terrestrial vertebrates; also sharks

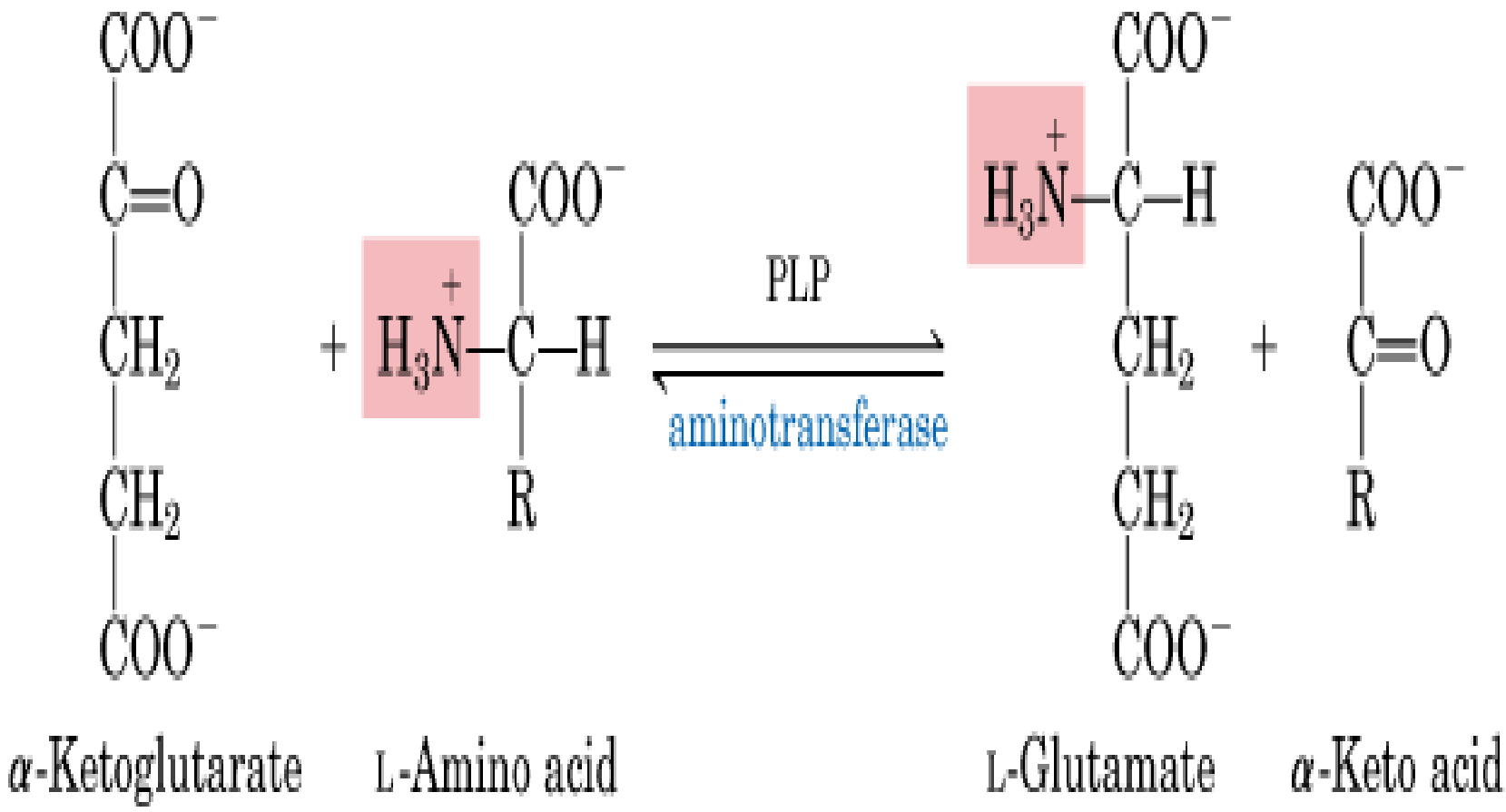
Uricotelic animals: birds, reptiles

(b)

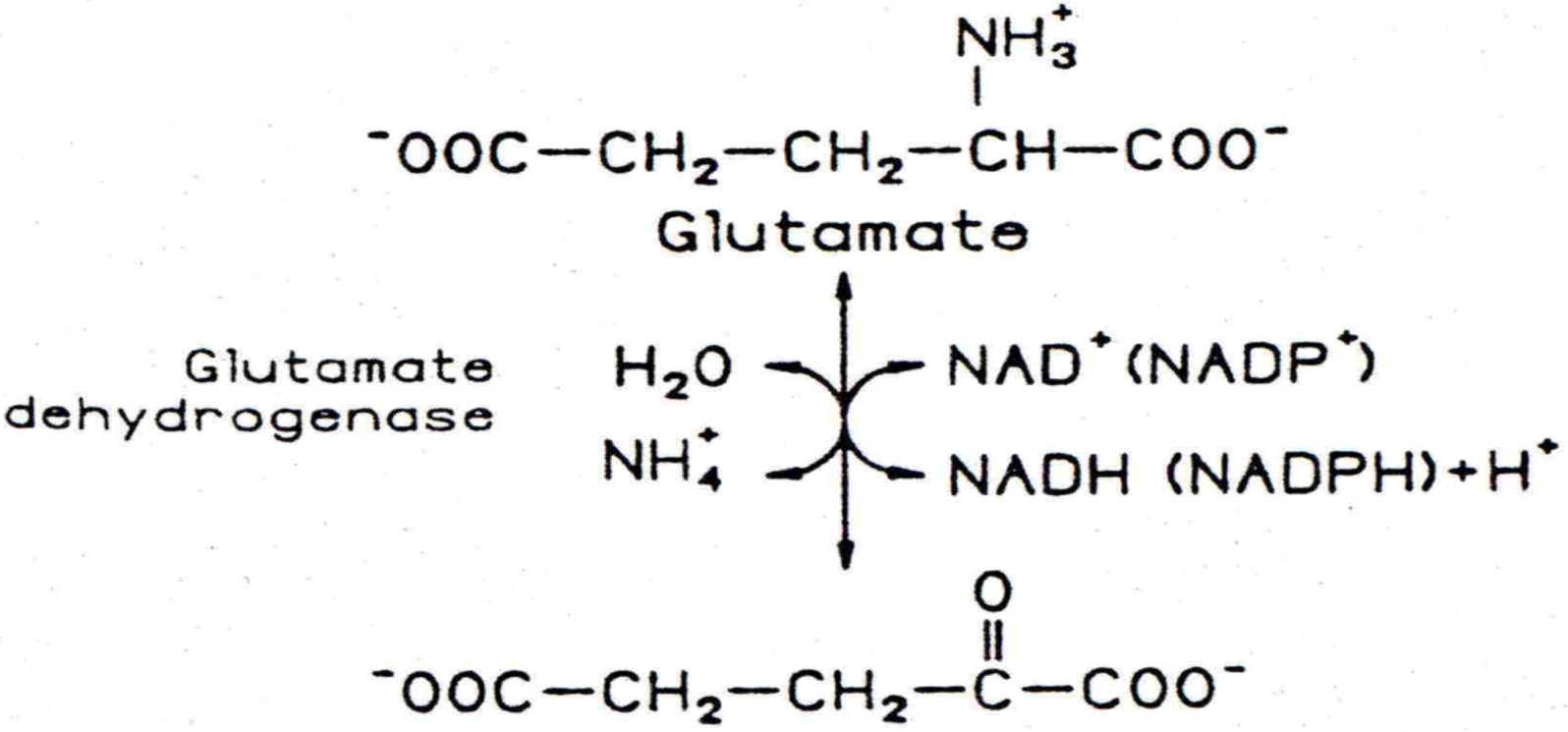

(a)
Gastric glands in stomach lining
Parietal cells (secrete HCl)
Chief cells (secrete pepsinogen)
Gastric mucosa (secretes gastrin)
Low pH
Stomach
Pepsinogen → pepsin
Pancreas
Pancreatic duct
pH 7
Zymogens → active proteases
(b)
Exocrine cells of pancreas
Rough ER
Zymogen granules
Collecting duct
(c)
Villi of small intestine
Small intestine
Villus
Intestinal mucosa (absorbs amino acids)

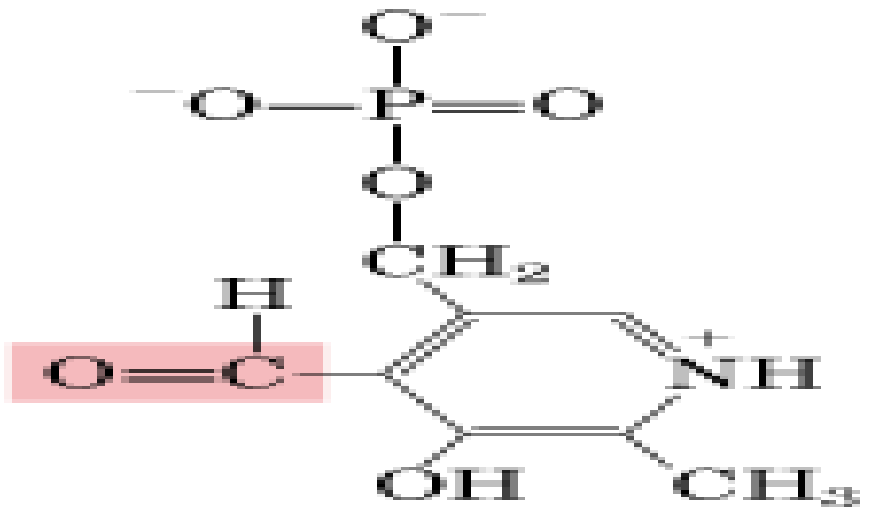
Transamination between amino acid and a-keto acid



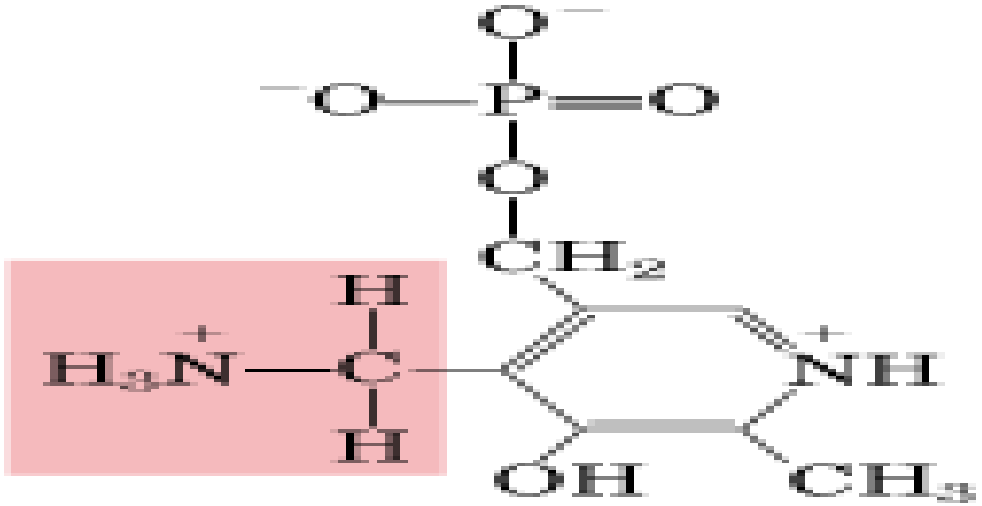

PLP
aminotransferase
α-Ketoglutarate
L-Amino acid
L-Glutamate
α-Keto acid

Oxidative deamination of glutamate and de novo synthesis of glutamate





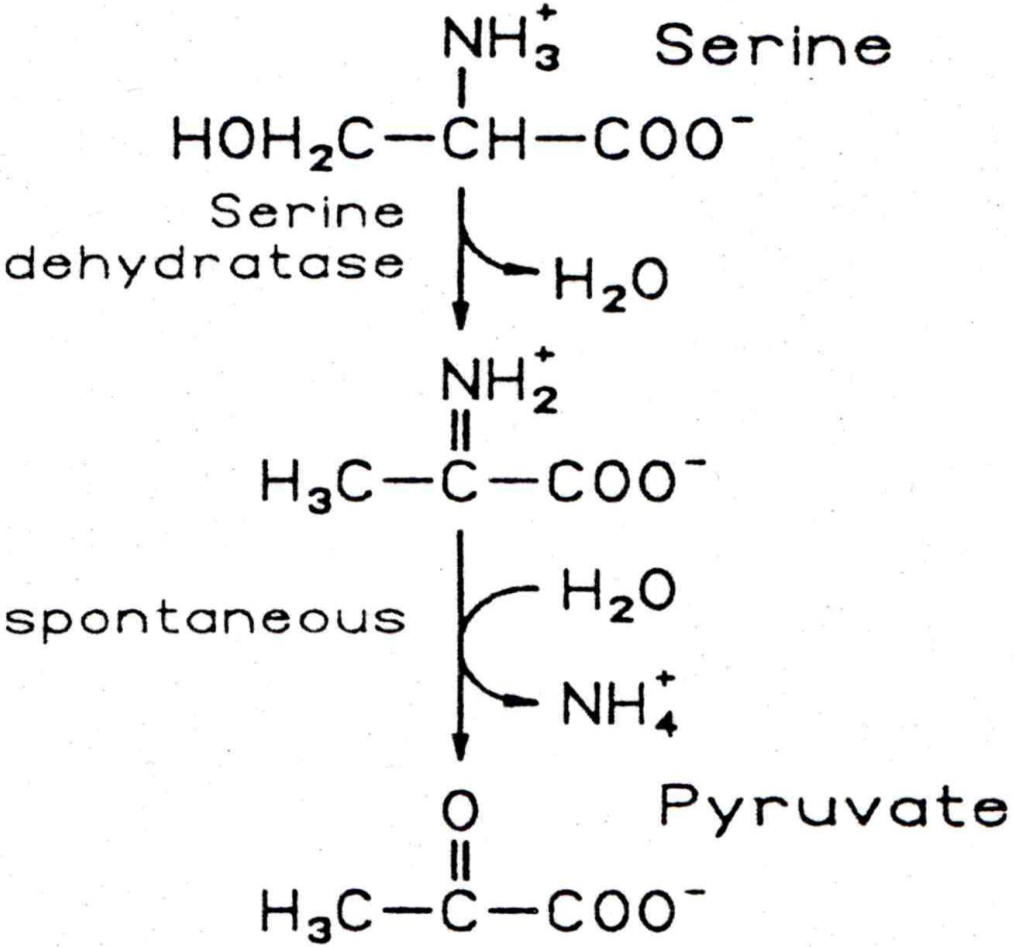
Pyridoxal phosphate
(PLP)

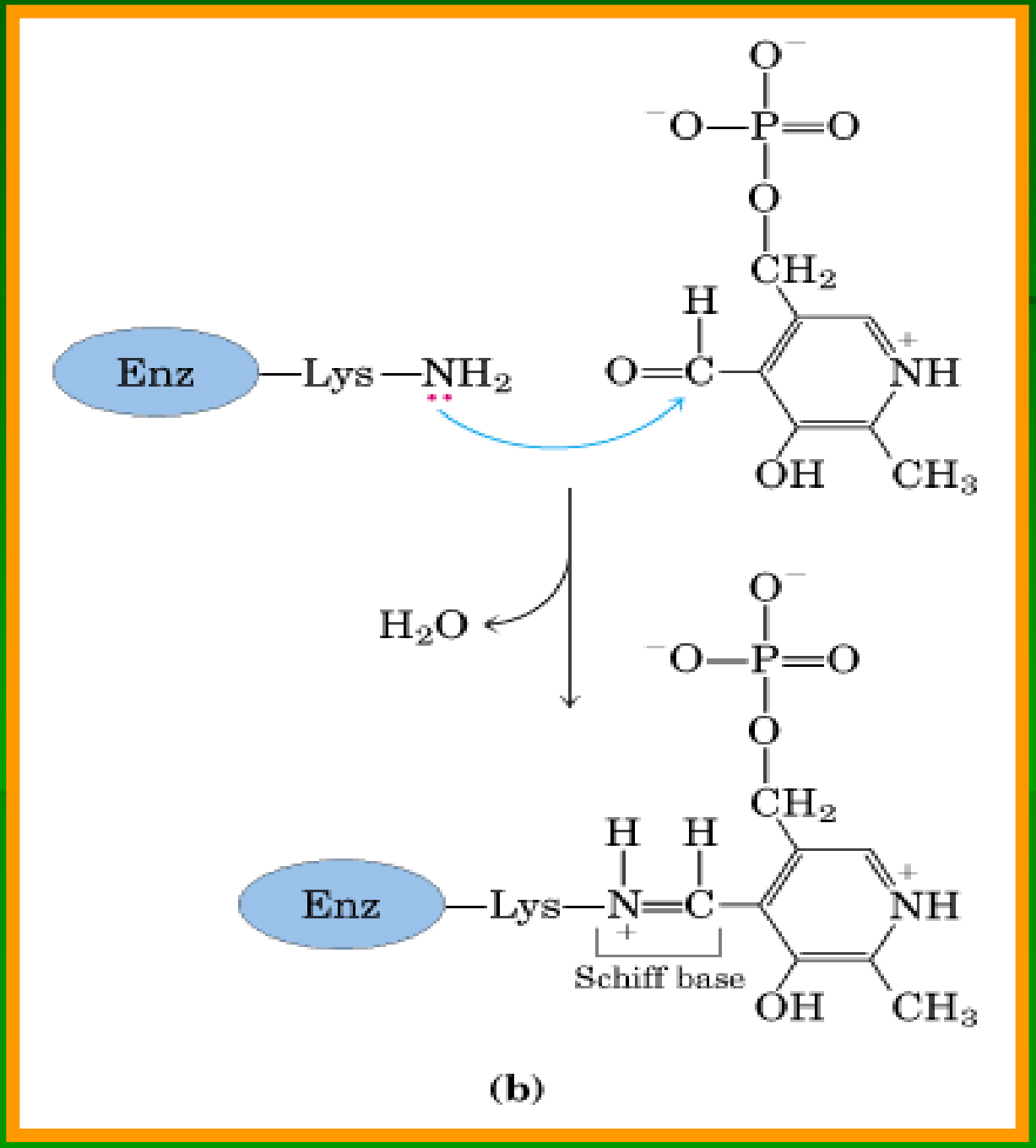


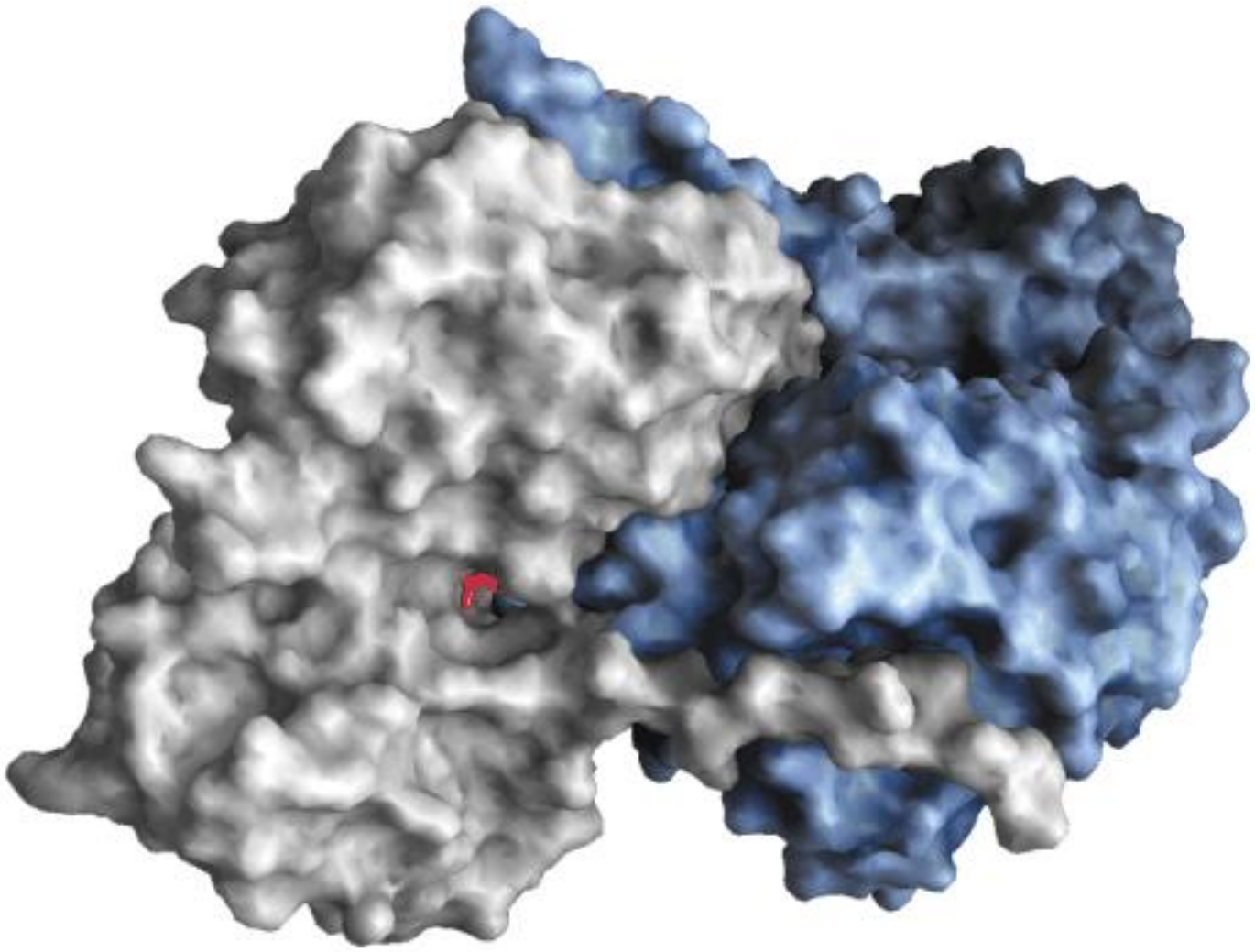
Pyridoxamine
phosphate

(a)

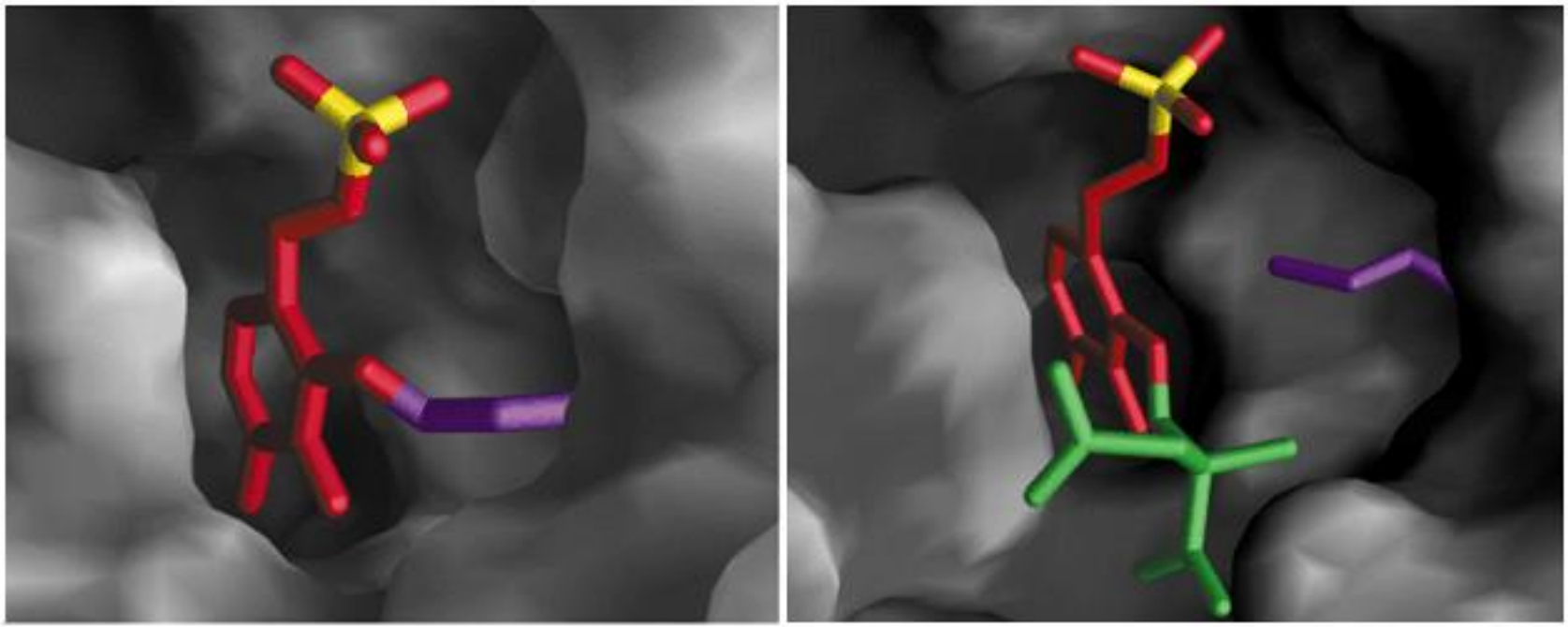
Deamination of serine by serine dehydratase



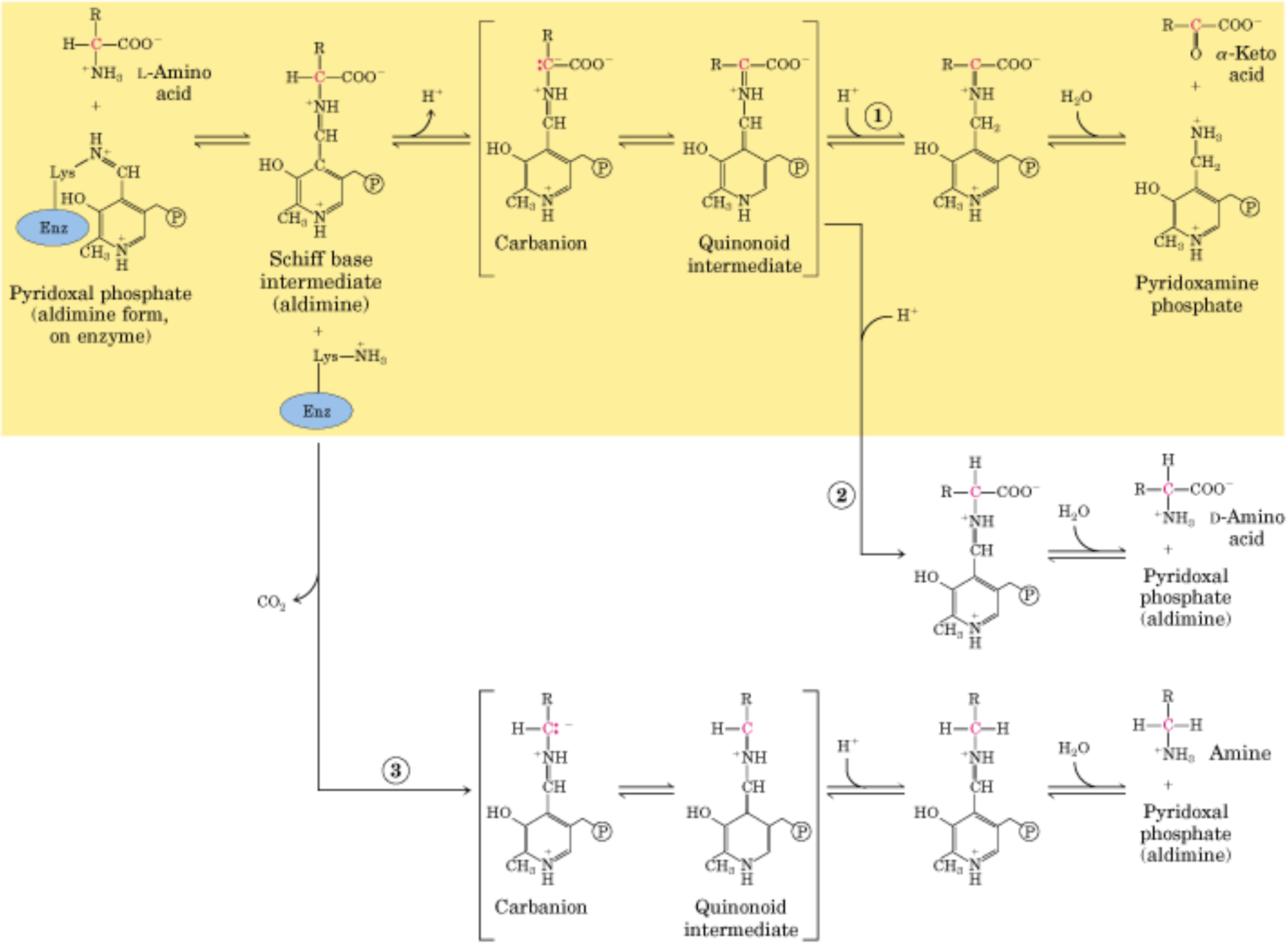

Enz
Lys
NH2
H2O
Enz
Lys
Schiff base
(b)



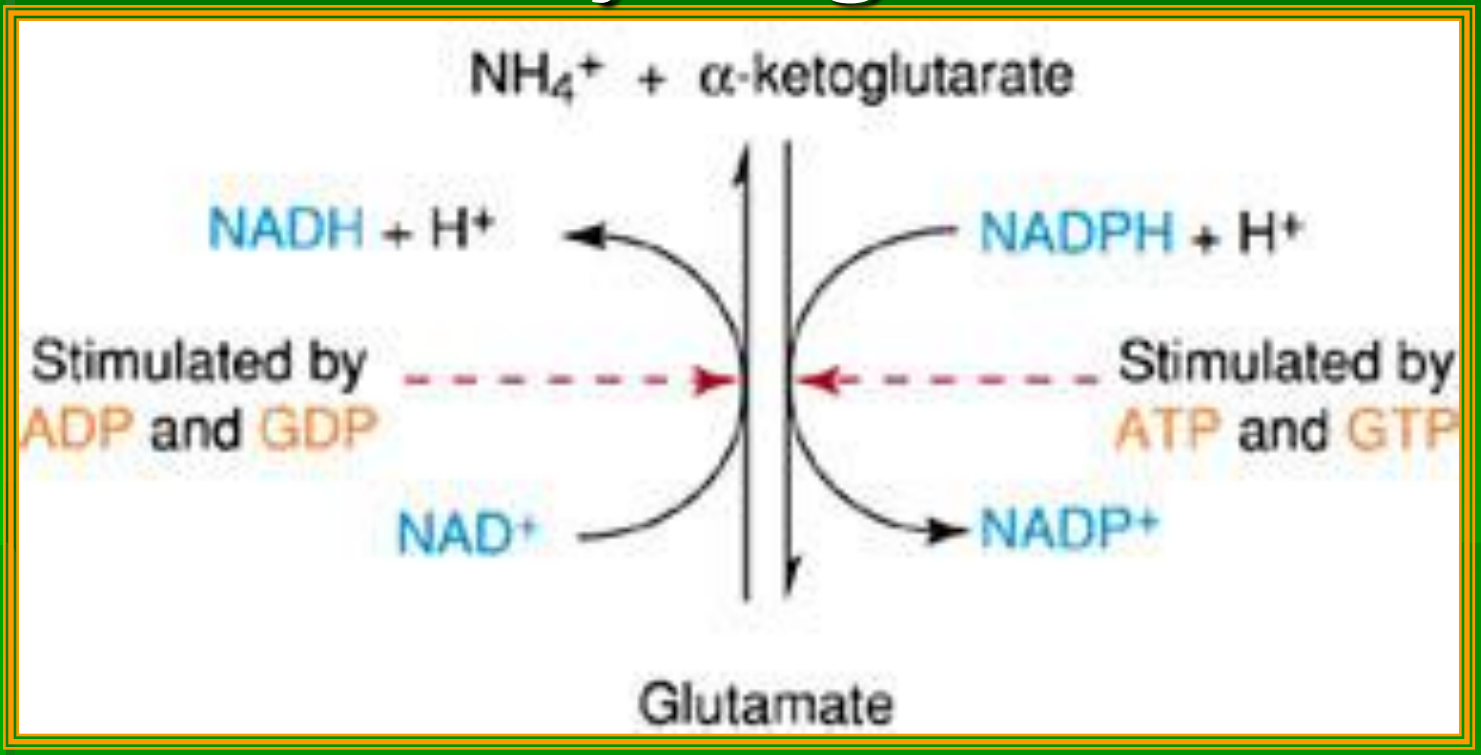
(c)

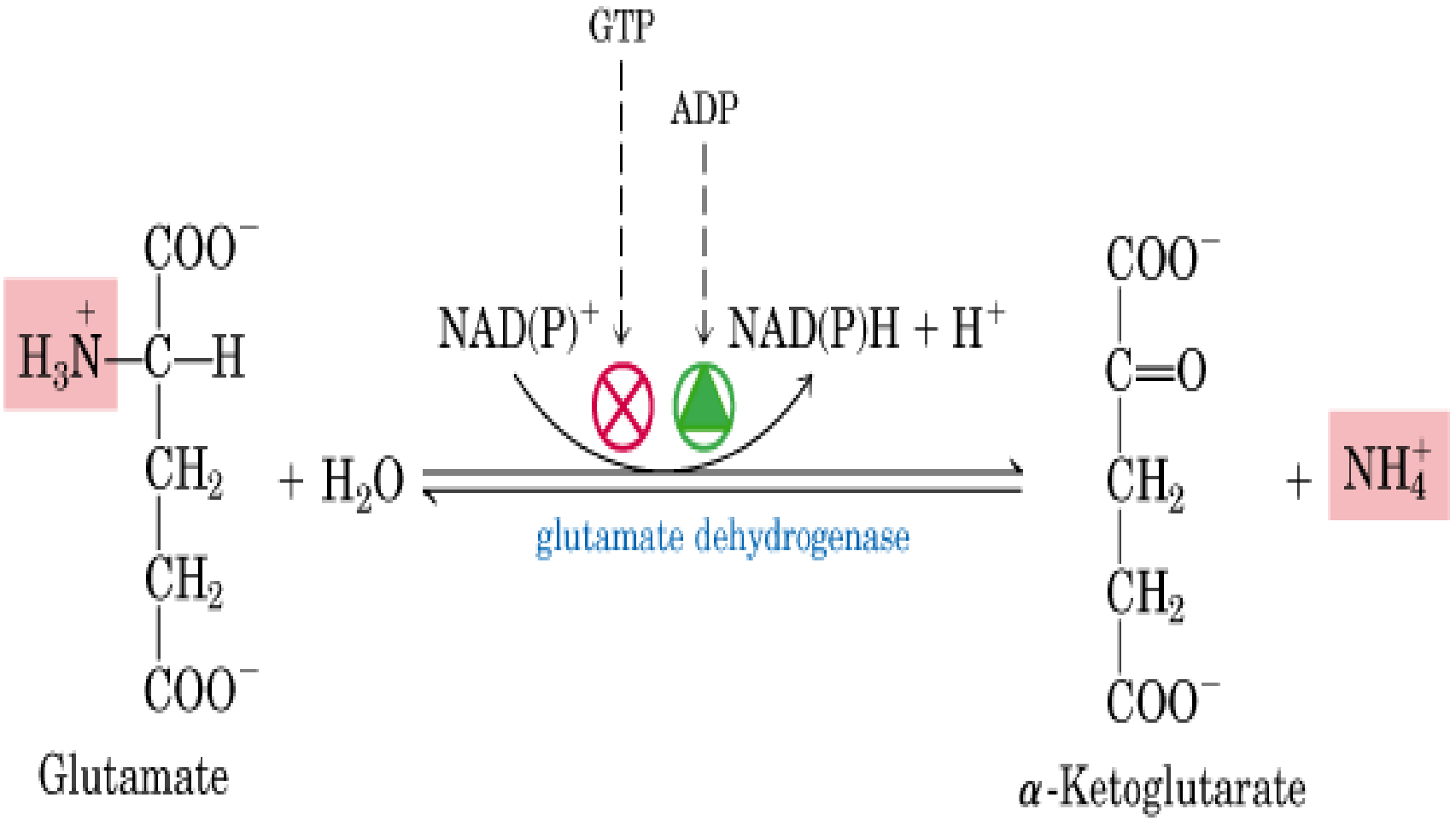


(d) (e)

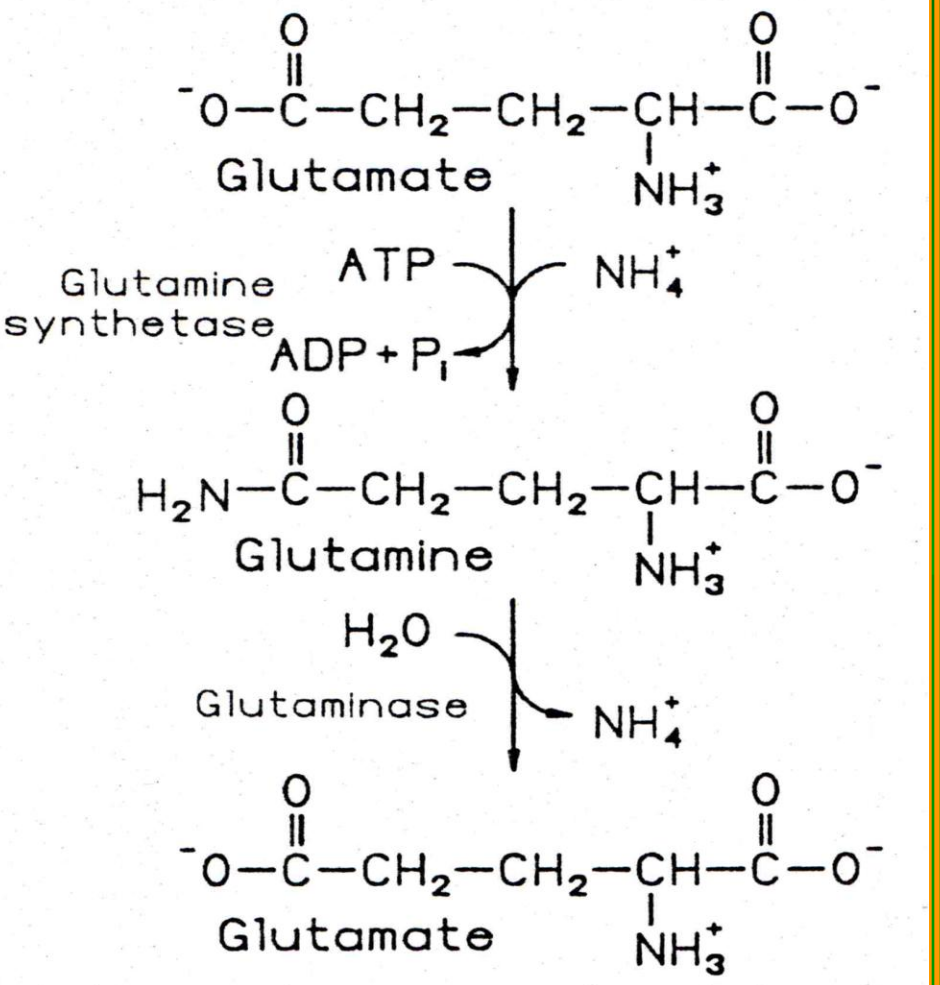

L-Amino acid
Lys
Enz
Pyridoxal phosphate (aldimine form, on enzyme)
Schiff base intermediate (aldimine)
Lys—NH3
Enz
H+
Carbanion
Quinonoid intermediate
H+
1
H2O
α-Keto acid
Pyridoxamine phosphate
H+
2
H2O
D-Amino acid
Pyridoxal phosphate (aldimine)
CO2
3
Carbanion
Quinonoid intermediate
H+
H2O
Amine
Pyridoxal phosphate (aldimine)

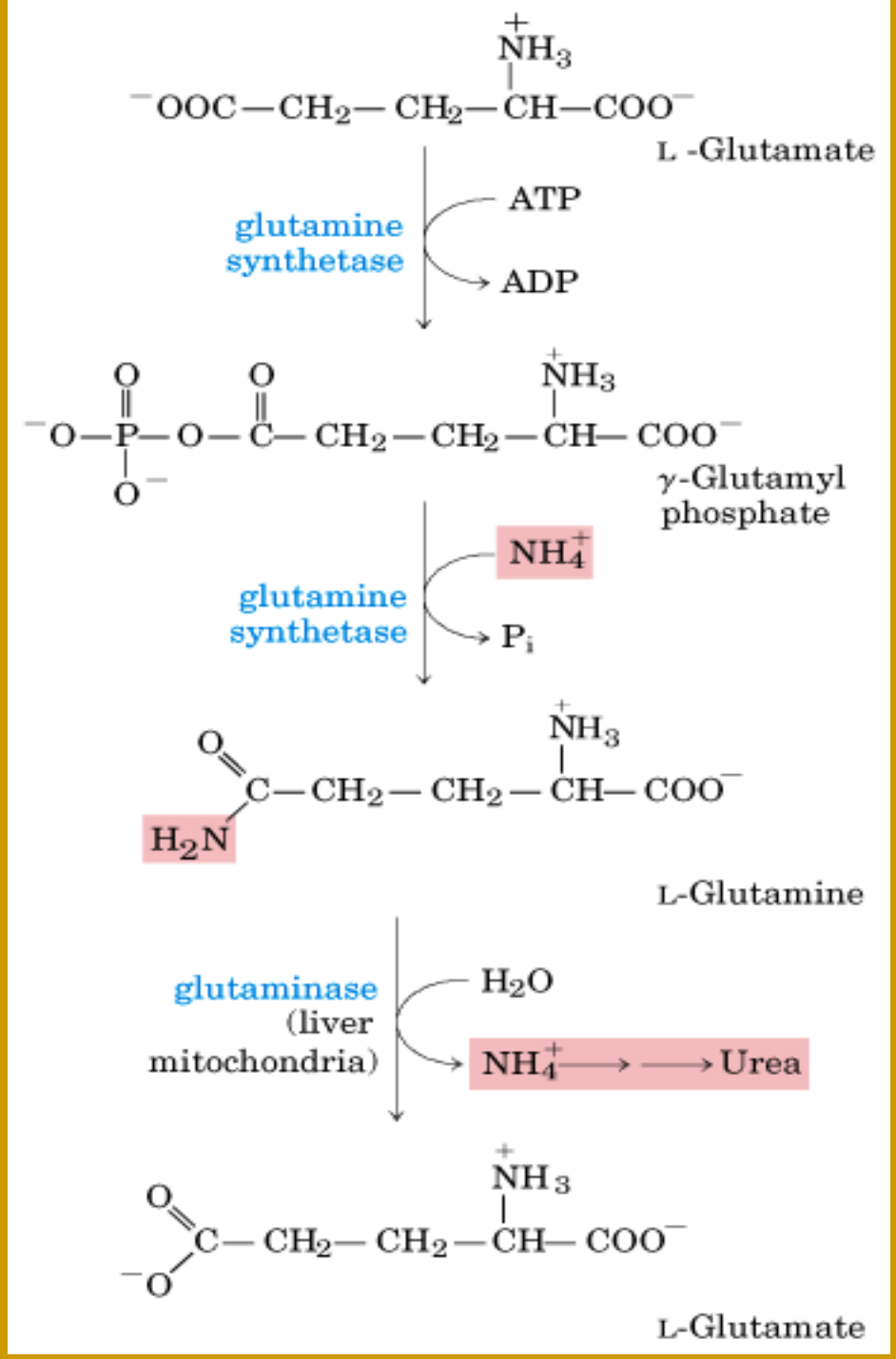
Regulation of glutamate dehydrogenase

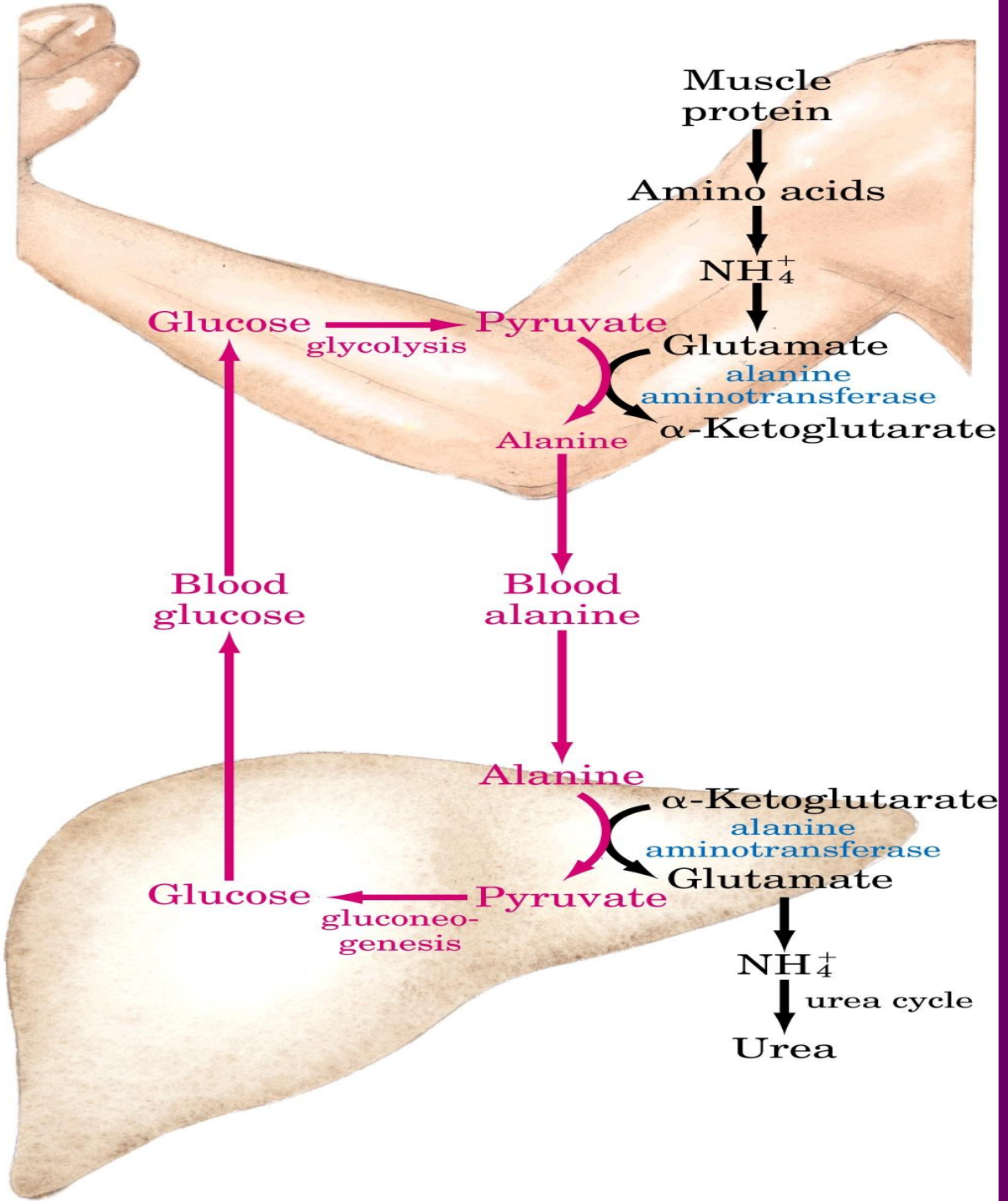



GTP
ADP
NAD(P)+
NAD(P)H + H+
+ H2O
glutamate dehydrogenase
+ NH4+
Glutamate
α-Ketoglutarate

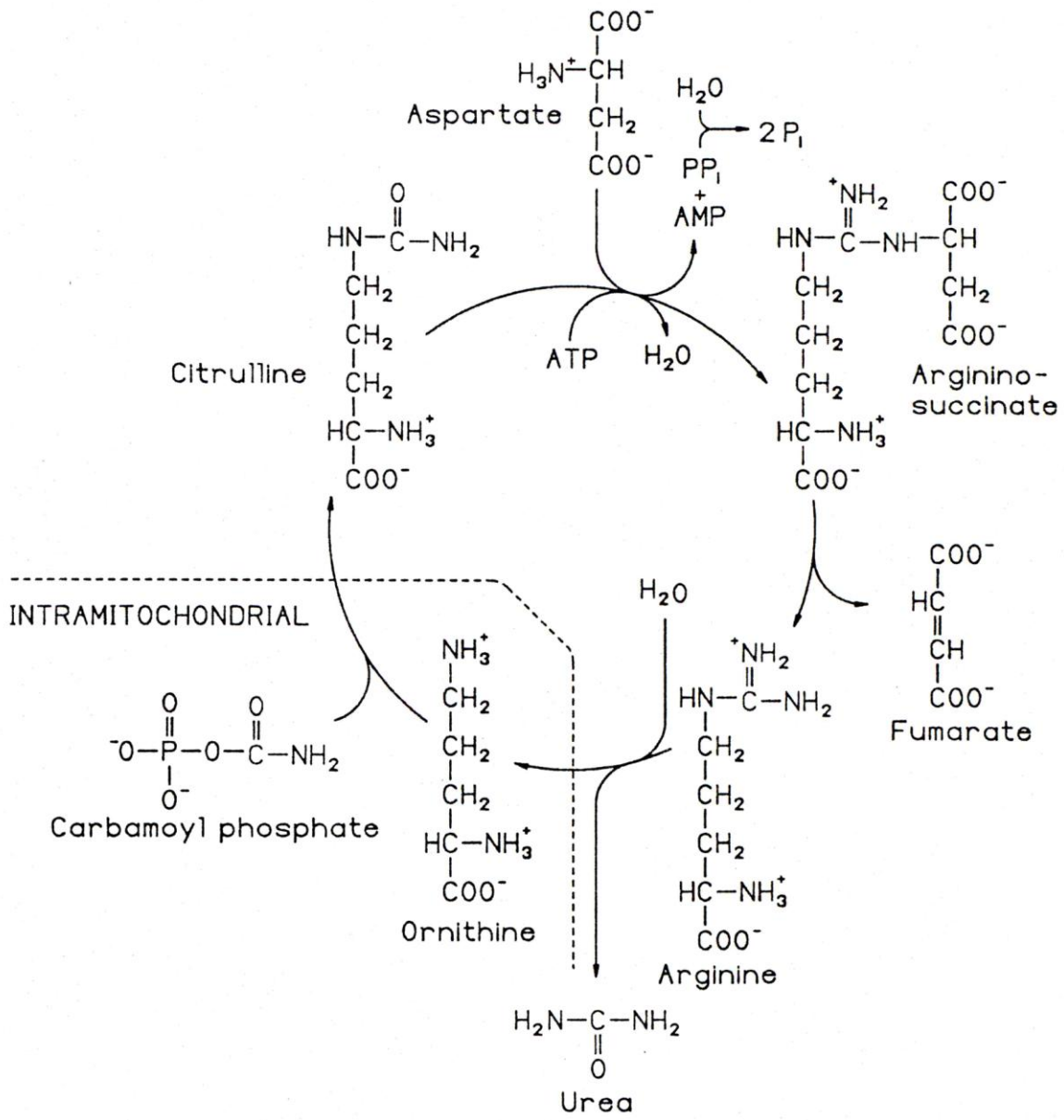
Glutamine as carrier of ammonium ions

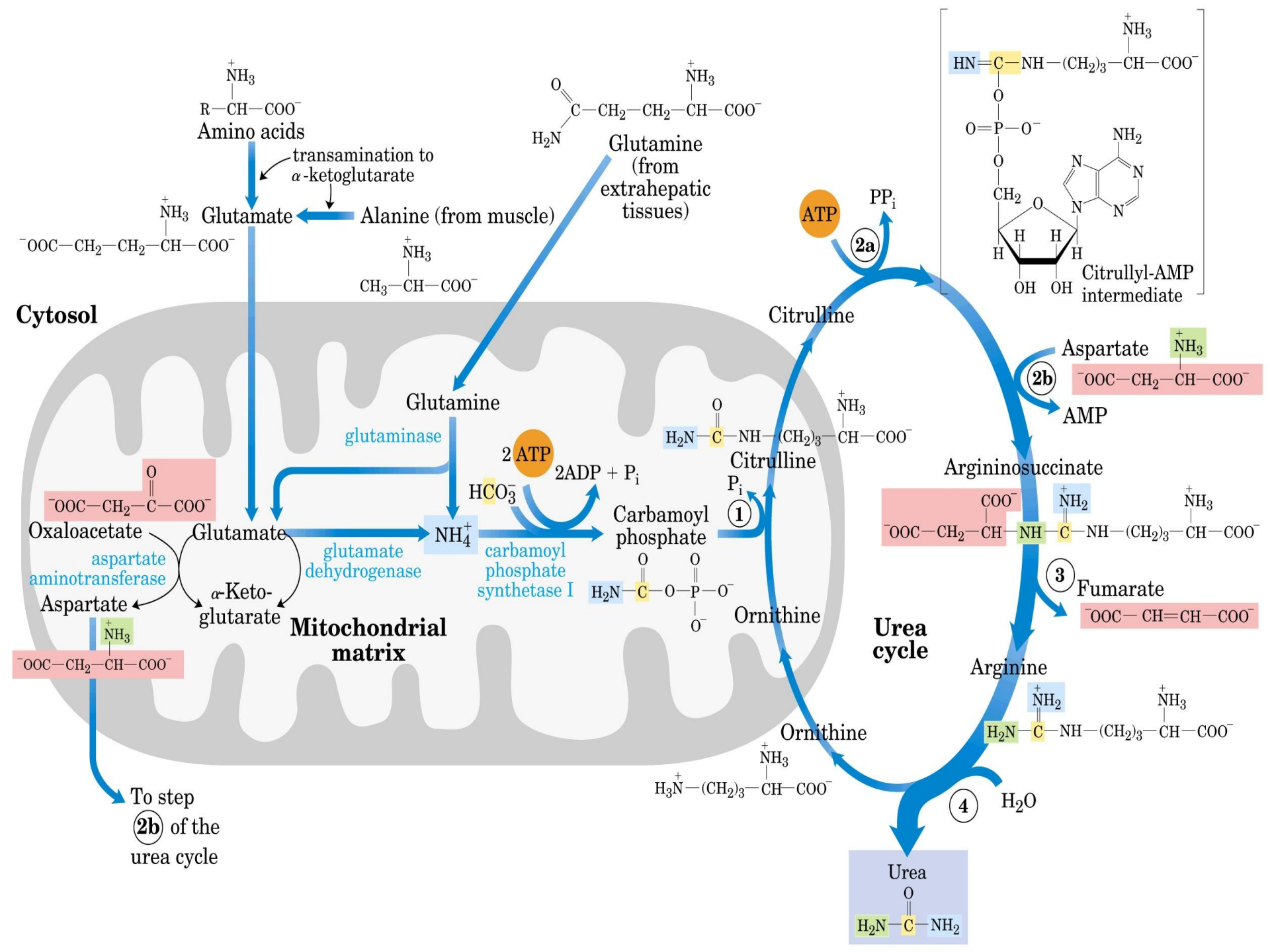



NH3
OOC—CH2—CH2—CH—COO
L -Glutamate
glutamine synthetase
ATP
ADP
NH3
O—P—O—C—CH2—CH2—CH—COO
γ-Glutamyl phosphate
glutamine synthetase
NH4+
Pi
NH3
C—CH2—CH2—CH—COO
H2N
L-Glutamine
glutaminase (liver mitochondria)
H2O
NH4+
Urea
NH3
C—CH2—CH2—CH—COO
L-Glutamate

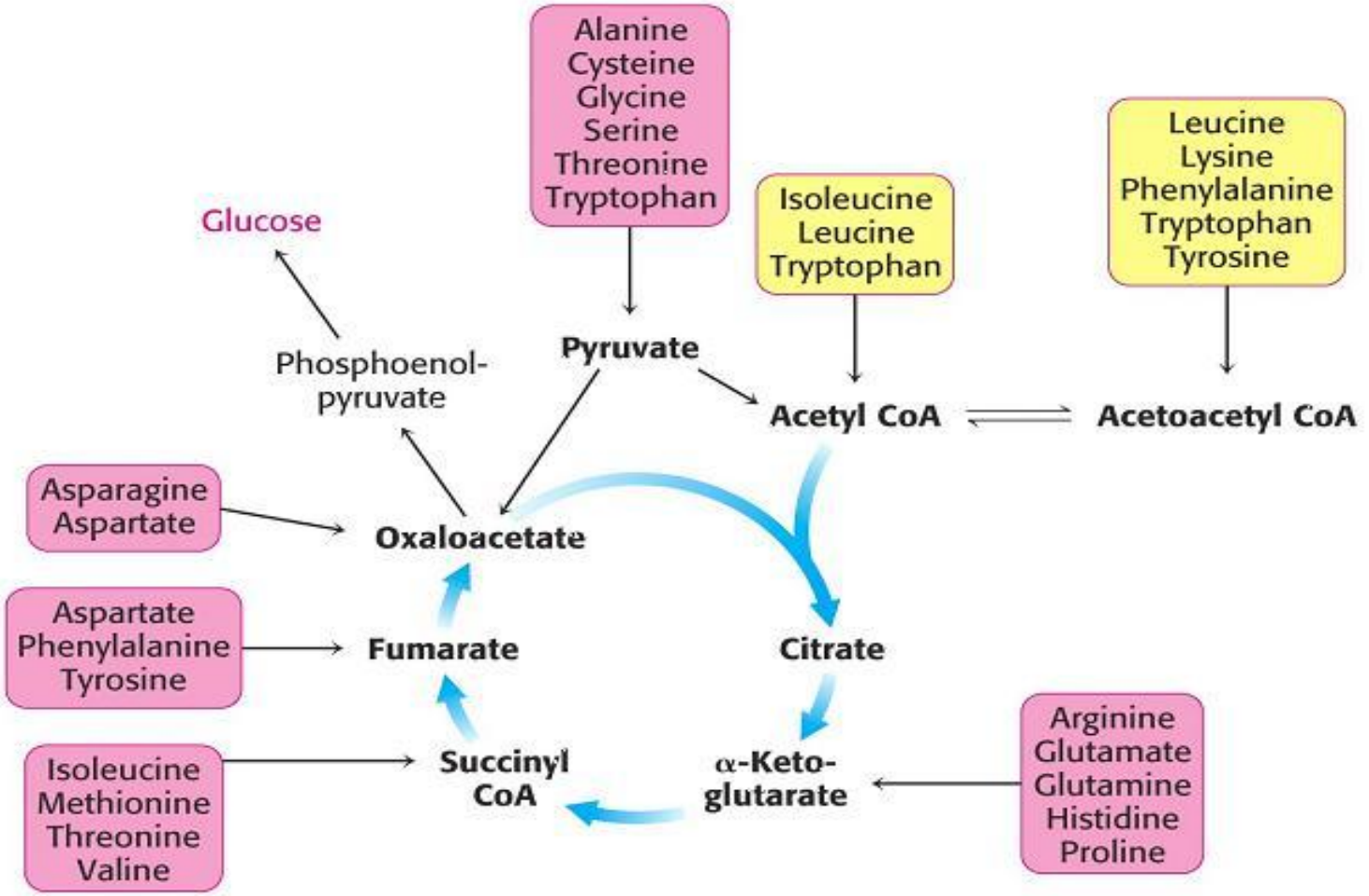

Muscle protein
Amino acids
NH_4^+
Glucose
glycolysis
Pyruvate
Glutamate
alanine aminotransferase
α-Ketoglutarate
Alanine
Blood glucose
Blood alanine
Alanine
α-Ketoglutarate
alanine aminotransferase
Glutamate
Glucose
gluconeo-genesis
Pyruvate
NH_4^+
urea cycle
Urea

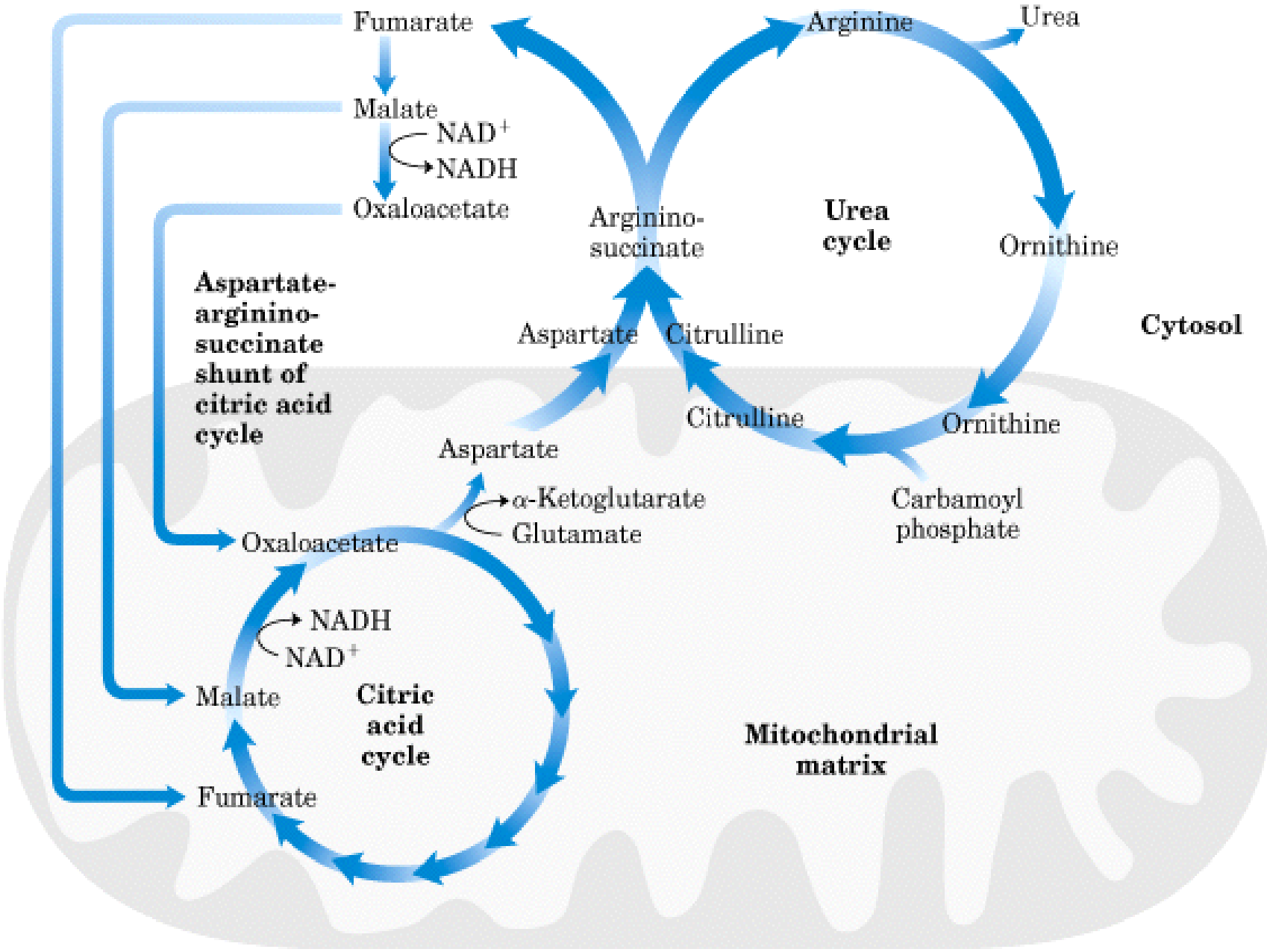
The urea cycle

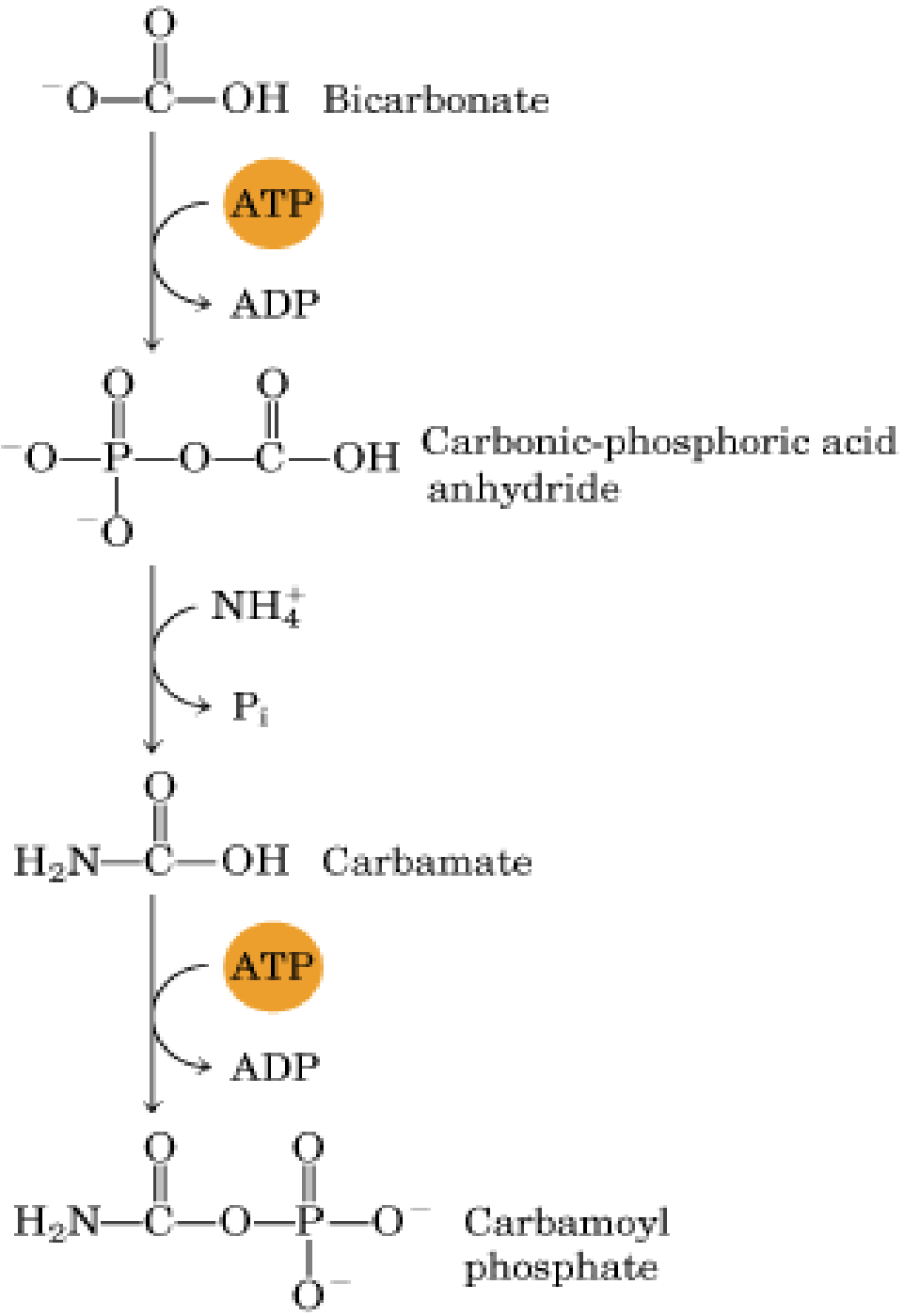


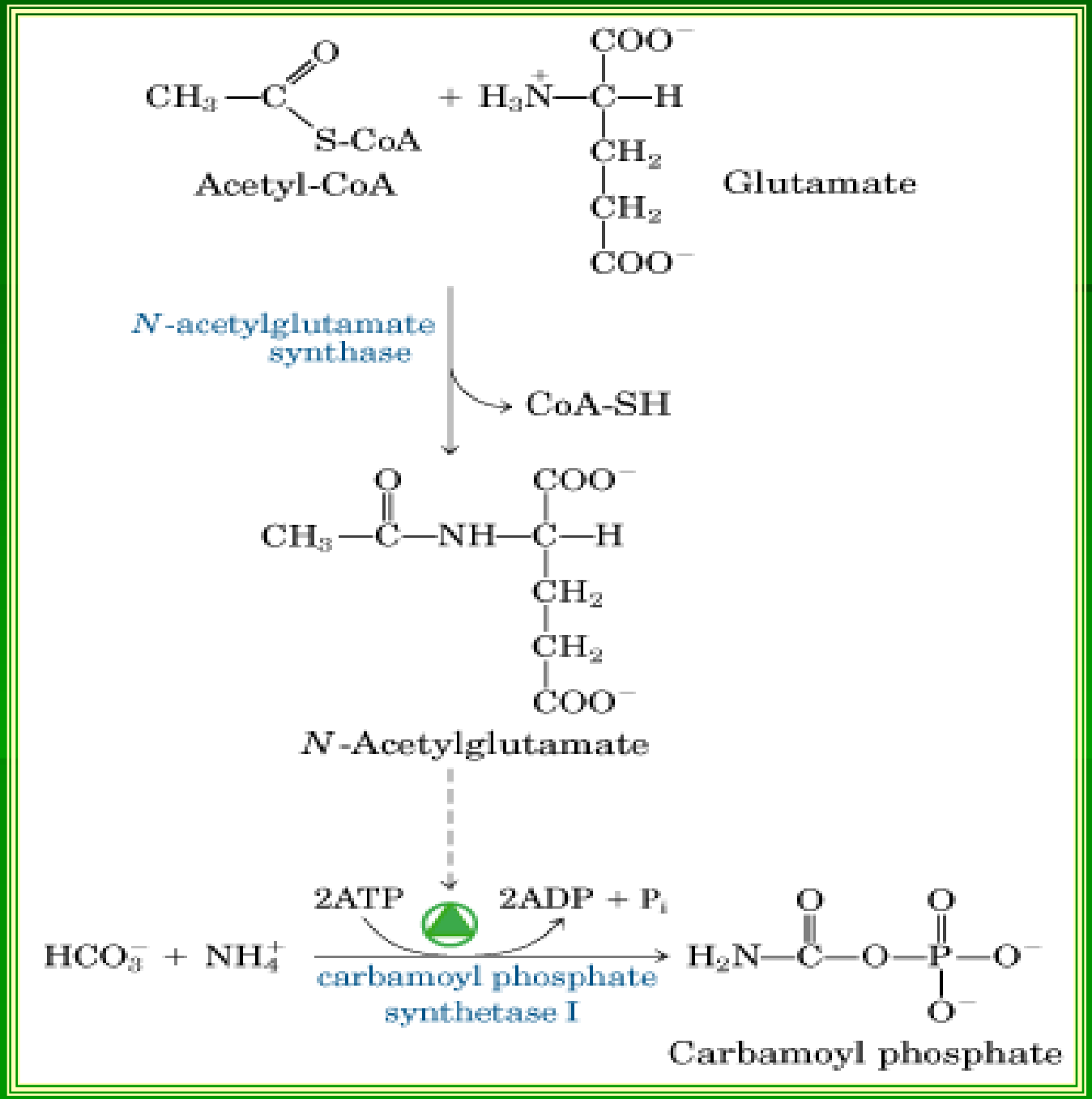

Amino acids
transamination to α-ketoglutarate
Glutamate
Alanine (from muscle)
Glutamine (from extrahepatic tissues)
Cytosol
Glutamine
glutaminase
2 ATP
2ADP + Pi
HCO3−
Oxaloacetate
Glutamate
NH4+
glutamate dehydrogenase
carbamoyl phosphate synthetase I
Carbamoyl phosphate
aspartate aminotransferase
α-Keto-glutarate
Aspartate
Mitochondrial matrix
To step 2b of the urea cycle
Citrulline
Pi
1
Ornithine
ATP
PPi
2a
Citrullyl-AMP intermediate
Aspartate
2b
AMP
Argininosuccinate
3
Fumarate
Urea cycle
Arginine
Ornithine
4
H2O
Urea

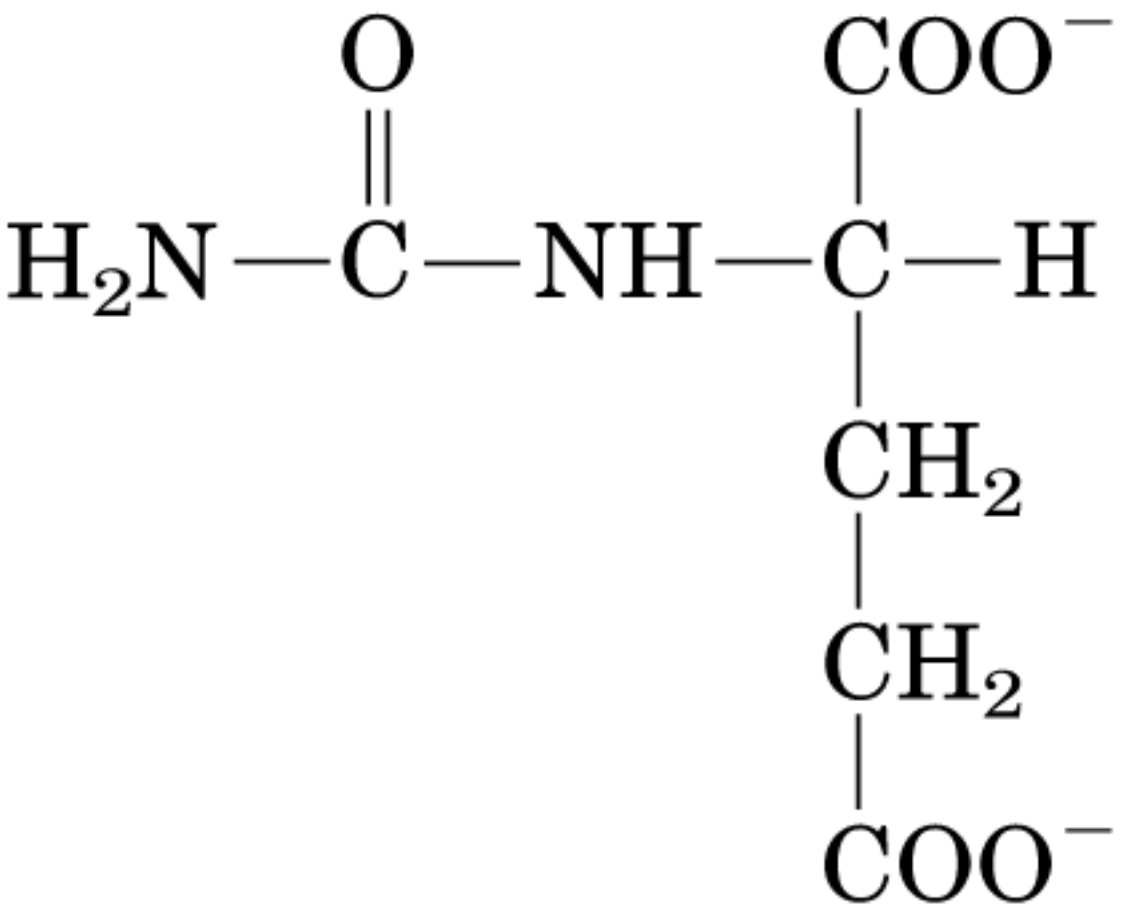
Entry of amino acid carbon skeletons into the TCA cycle




Fumarate
Malate
NAD+
NADH
Oxaloacetate
Arginino-
succinate
Arginine
Urea
Urea
cycle
Ornithine
Aspartate-
arginino-
succinate
shunt of
citric acid
cycle
Aspartate
Citrulline
Cytosol
Citrulline
Ornithine
Aspartate
α-Ketoglutarate
Glutamate
Carbamoyl
phosphate
Oxaloacetate
NADH
NAD+
Malate
Citric
acid
cycle
Mitochondrial
matrix
Fumarate

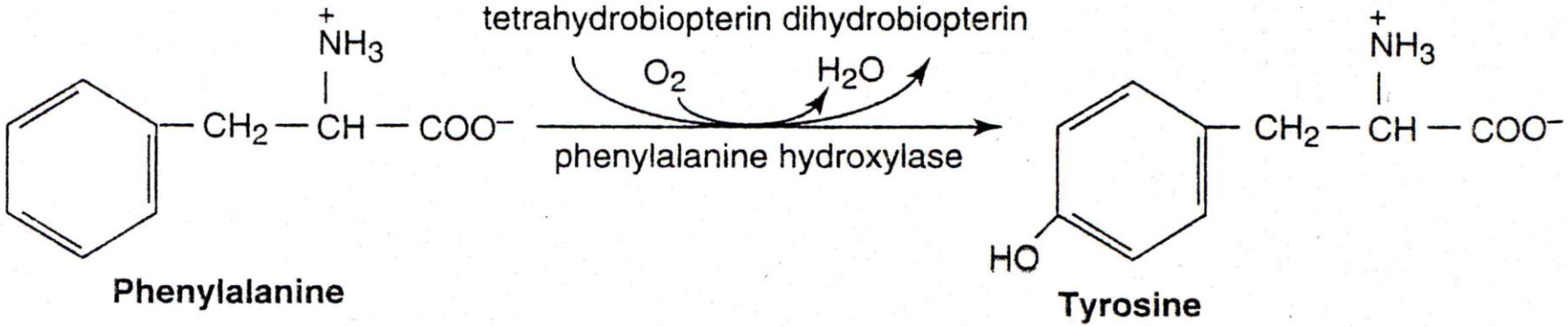

Bicarbonate
ATP
ADP
Carbonic-phosphoric acid anhydride
NH_4^+
P_i
Carbamate
ATP
ADP
Carbamoyl phosphate

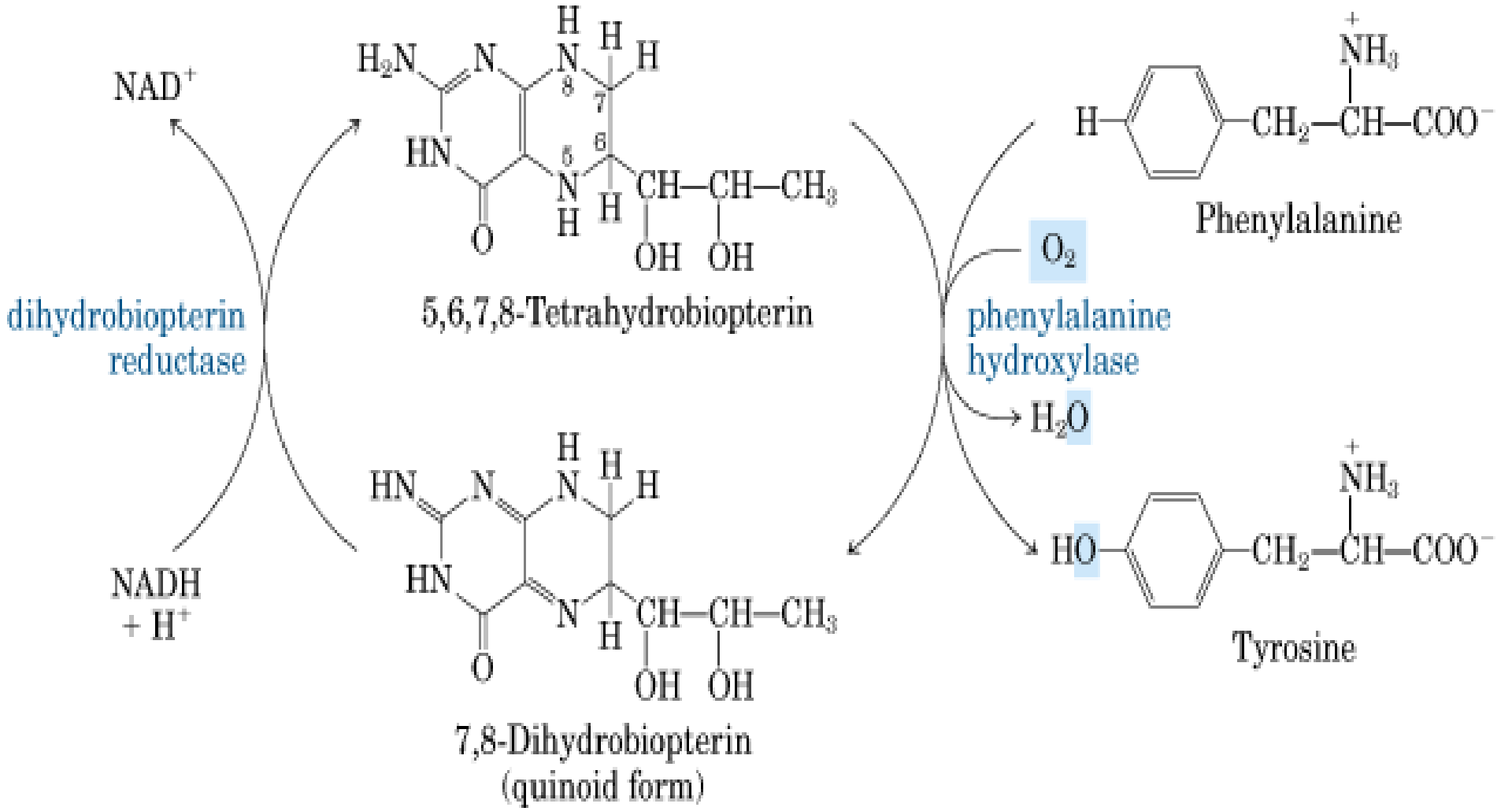

Acetyl-CoA
Glutamate
N-acetylglutamate synthase
CoA-SH
N-Acetylglutamate
2ATP
2ADP + Pi
carbamoyl phosphate synthetase I
Carbamoyl phosphate



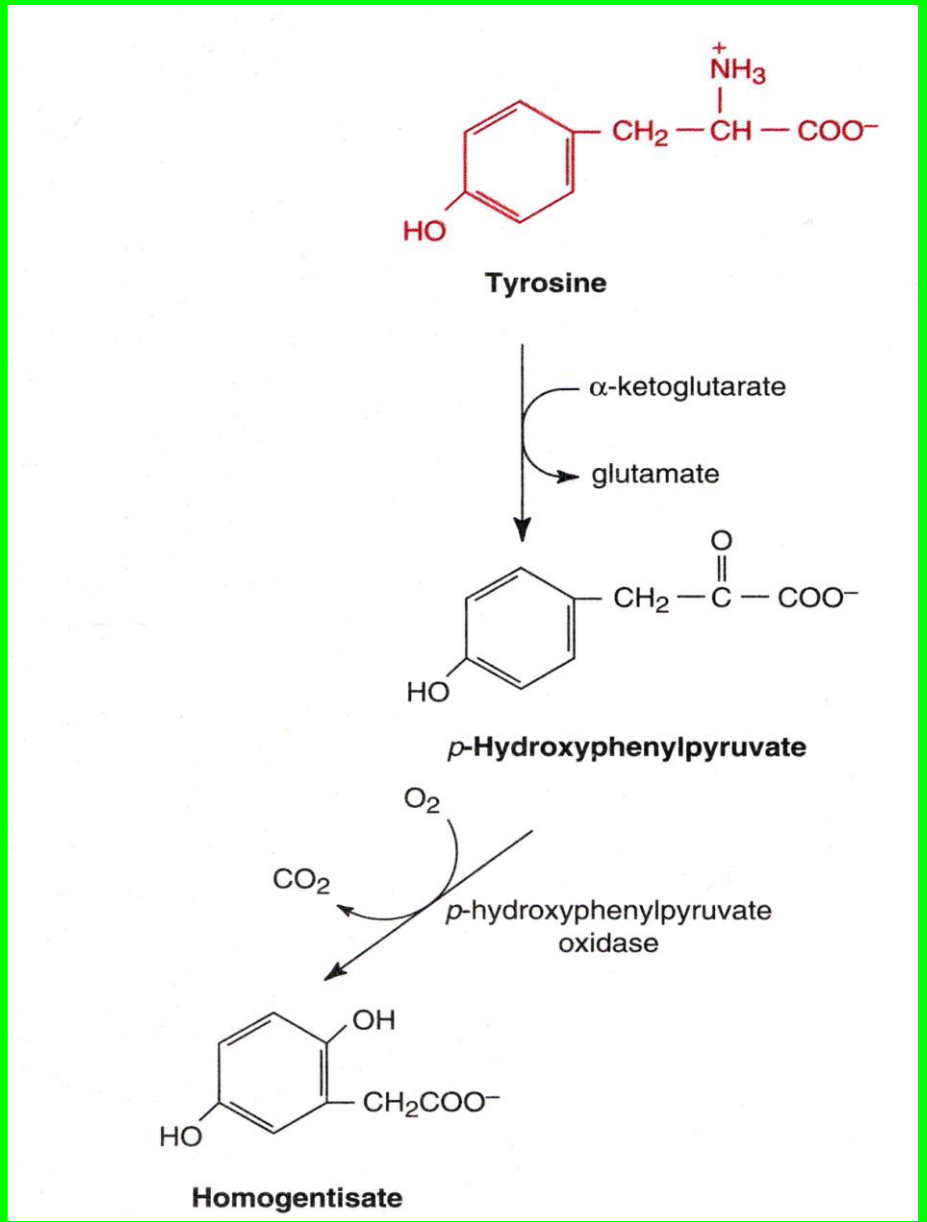
Carbamoyl glutamate

Phenylalanine hydroxylase converts Phe into Tyr




NAD+
NADH
+ H+
dihydrobiopterin
reductase
5,6,7,8-Tetrahydrobiopterin
7,8-Dihydrobiopterin
(quinoid form)
O2
H2O
phenylalanine
hydroxylase
Phenylalanine
Tyrosine

Degradation of tyrosine



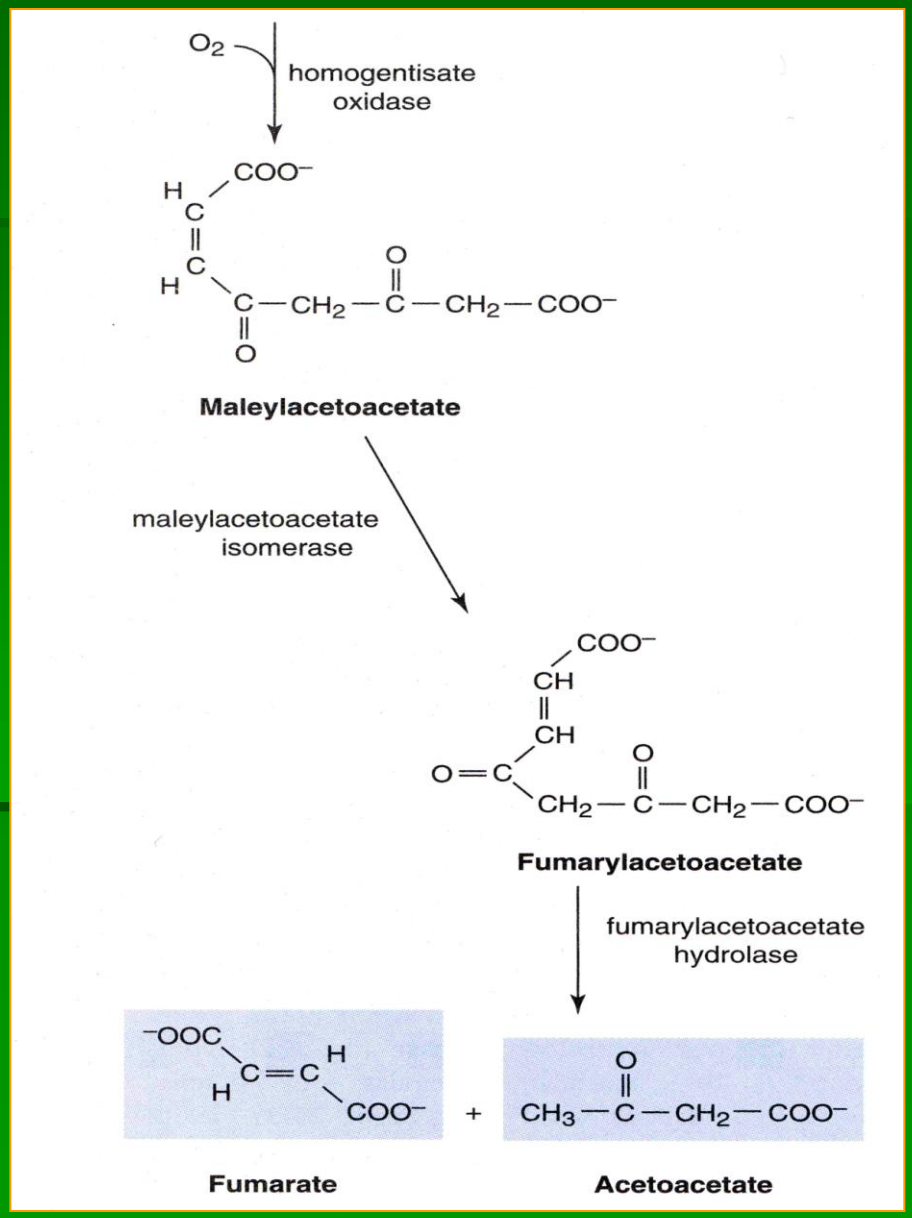
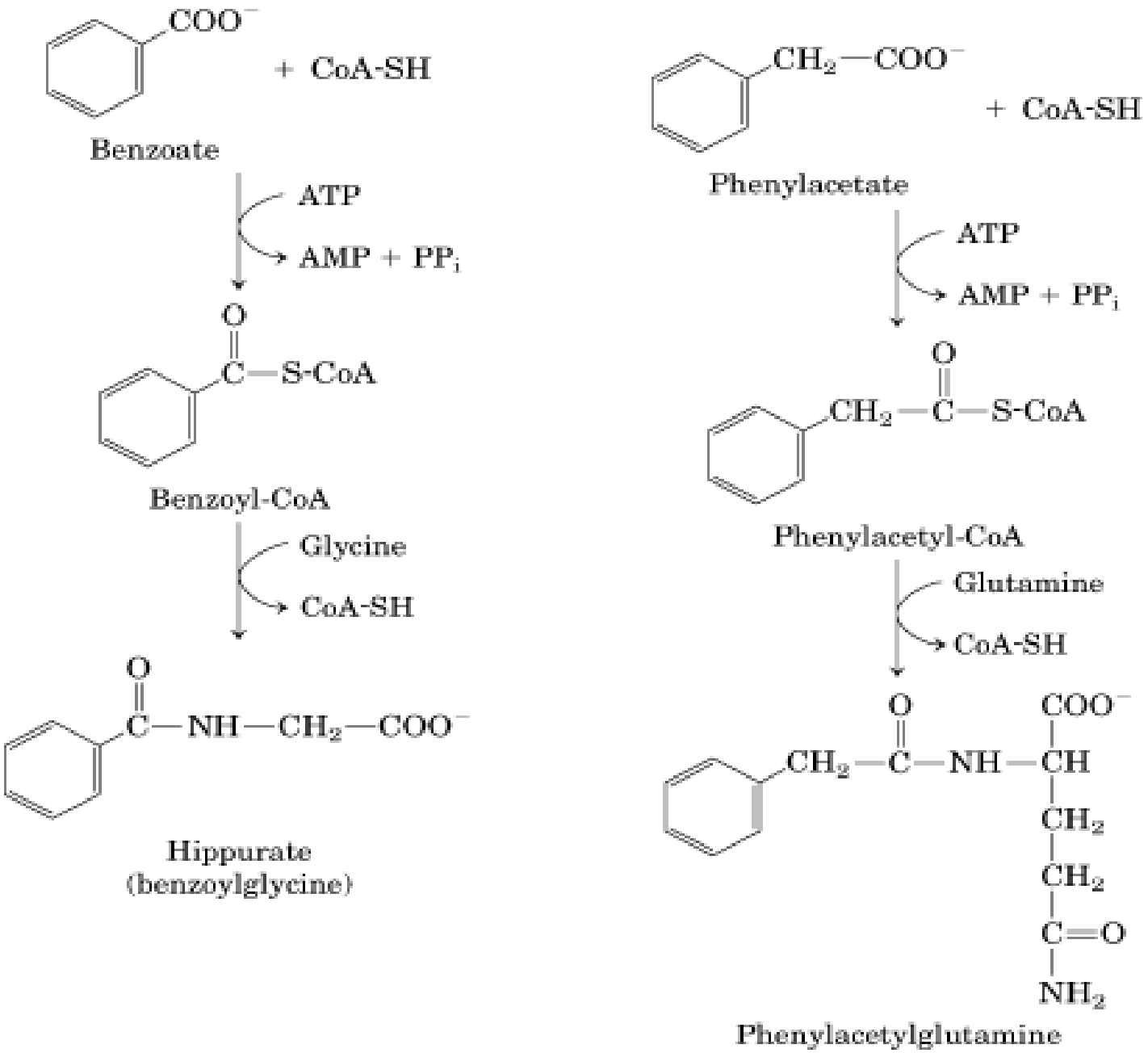


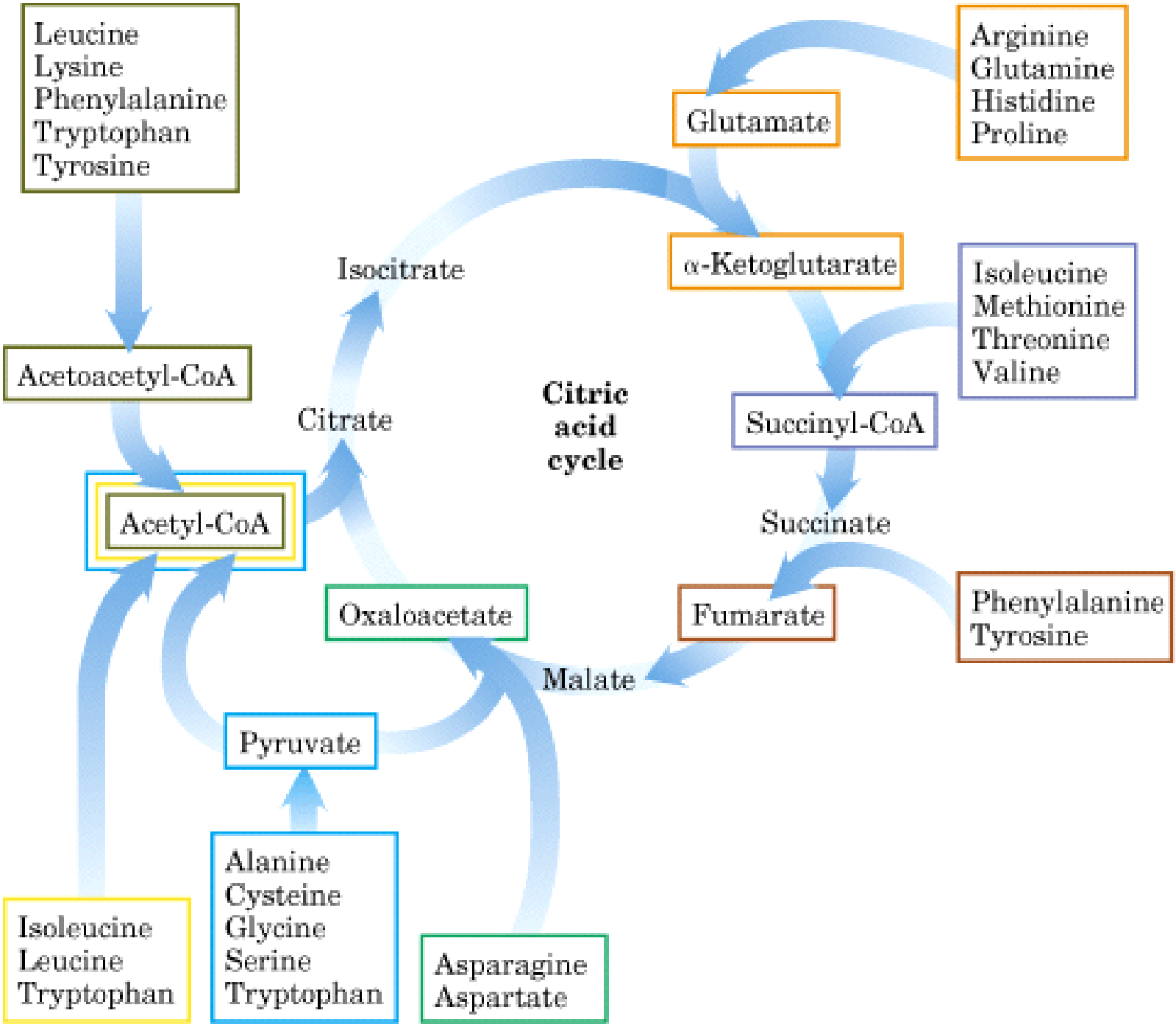
table 18–1

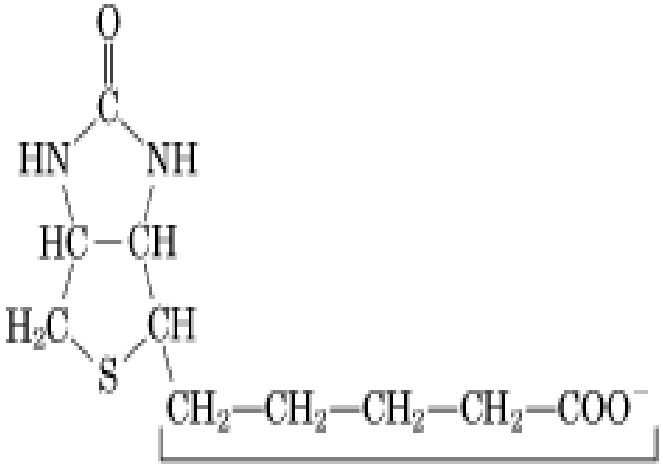
Nonessential and Essential Amino Acids for Humans and the Albino Rat

Nonessential	Essential
Alanine	Arginine*
Asparagine	Histidine
Aspartate	Isoleucine
Cysteine	Leucine
Glutamate	Lysine
Glutamine	Methionine
Glycine	Phenylalanine
Proline	Threonine
Serine	Tryptophan
Tyrosine	Valine

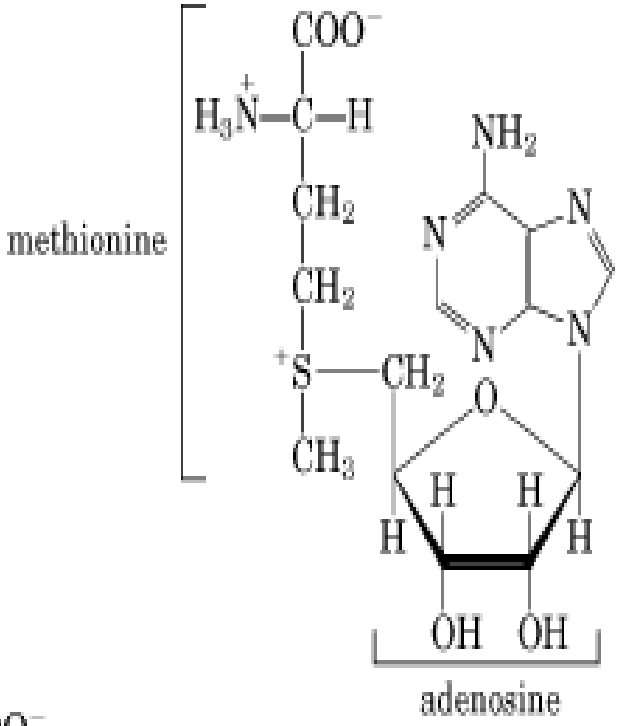
*Essential in young, growing animals but not in adults.


COO⁻
+ CoA-SH
Benzoate
ATP
AMP + PPi
O
C—S-CoA
Benzoyl-CoA
Glycine
CoA-SH
O
C—NH—CH2—COO⁻
Hippurate
(benzoylglycine)
CH2—COO⁻
+ CoA-SH
Phenylacetate
ATP
AMP + PPi
O
CH2—C—S-CoA
Phenylacetyl-CoA
Glutamine
CoA-SH
O
CH2—C—NH—CH
COO⁻
CH2
CH2
C=O
NH2
Phenylacetylglutamine

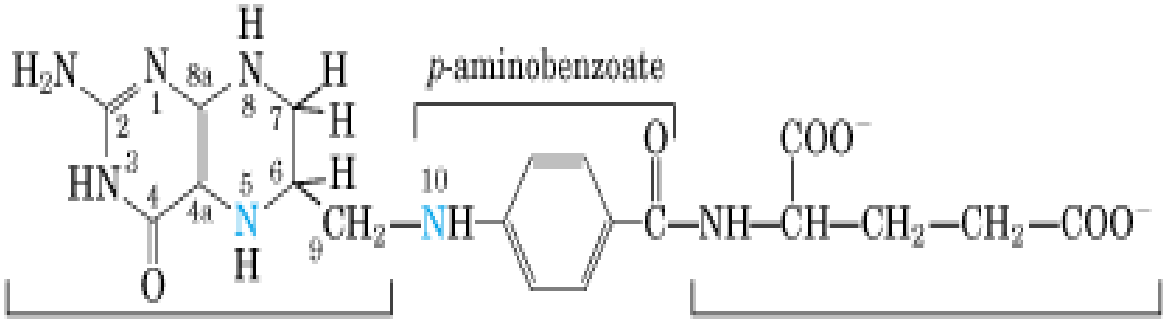

Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Arginine
Glutamine
Histidine
Proline
Glutamate
α-Ketoglutarate
Isocitrate
Isoleucine
Methionine
Threonine
Valine
Acetoacetyl-CoA
Citrate
Citric acid cycle
Succinyl-CoA
Acetyl-CoA
Succinate
Oxaloacetate
Fumarate
Phenylalanine
Tyrosine
Malate
Pyruvate
Alanine
Cysteine
Glycine
Serine
Tryptophan
Isoleucine
Leucine
Tryptophan
Asparagine
Aspartate



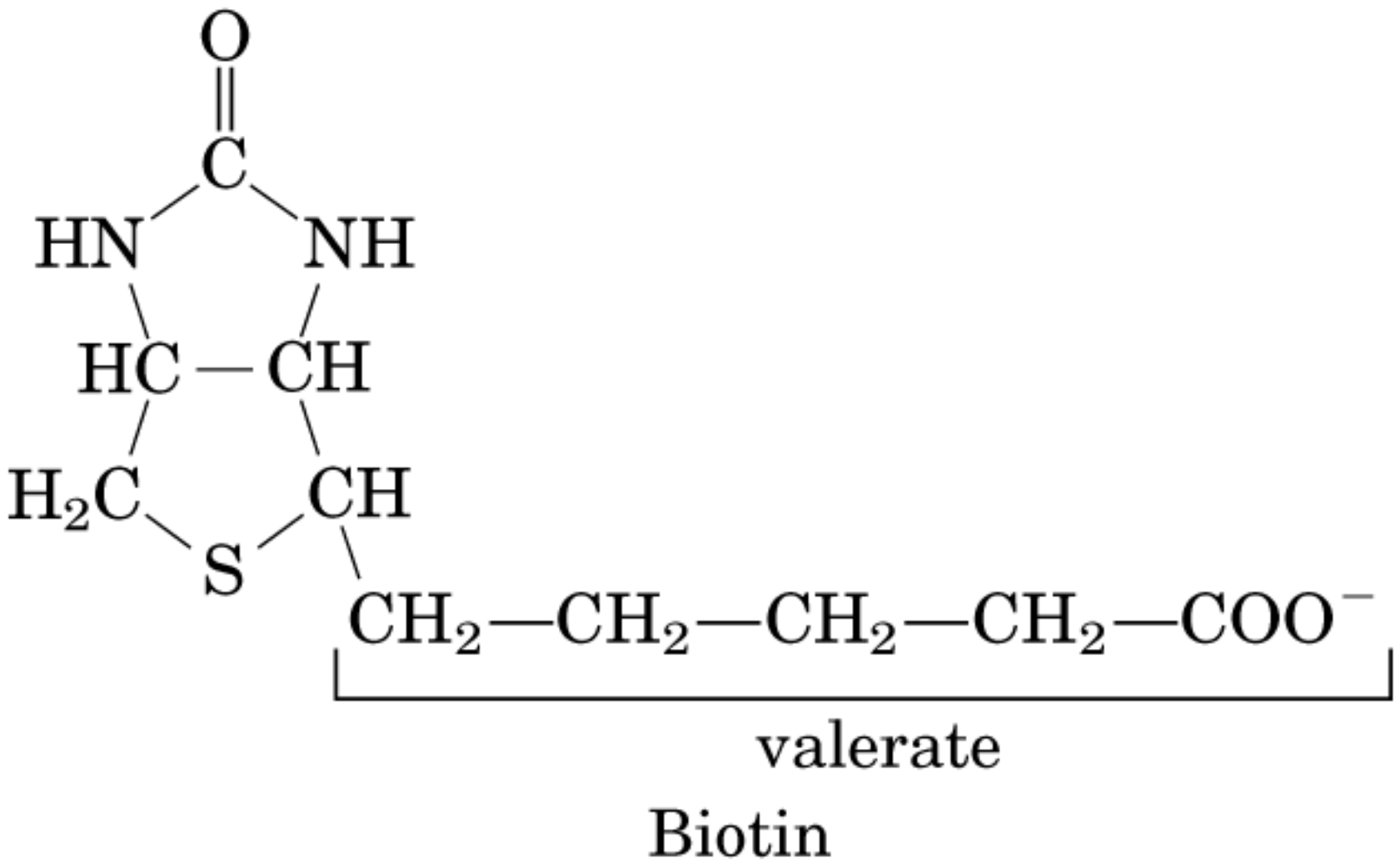
Biotin



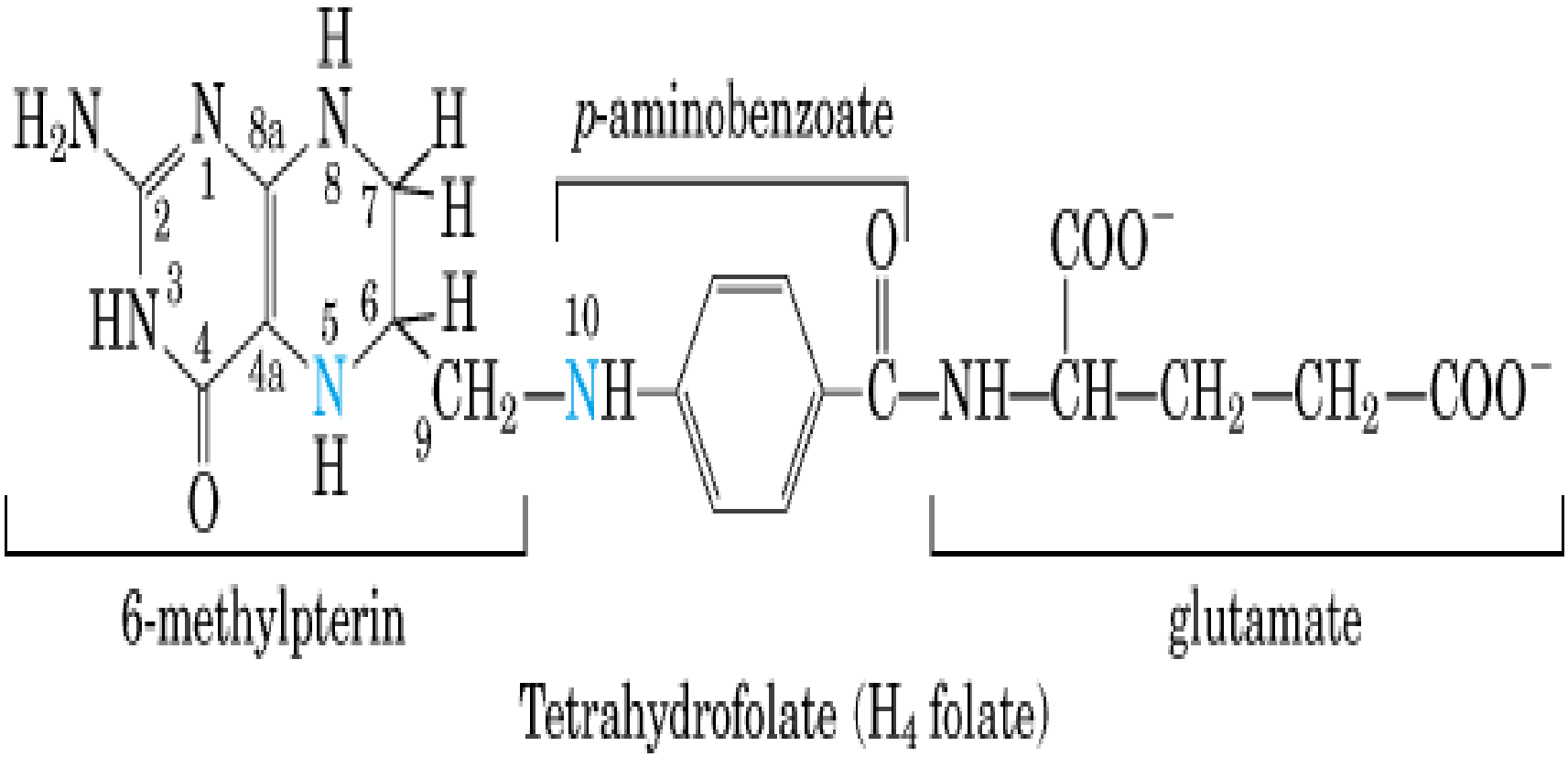
S-Adenosylmethionine (adoMet)



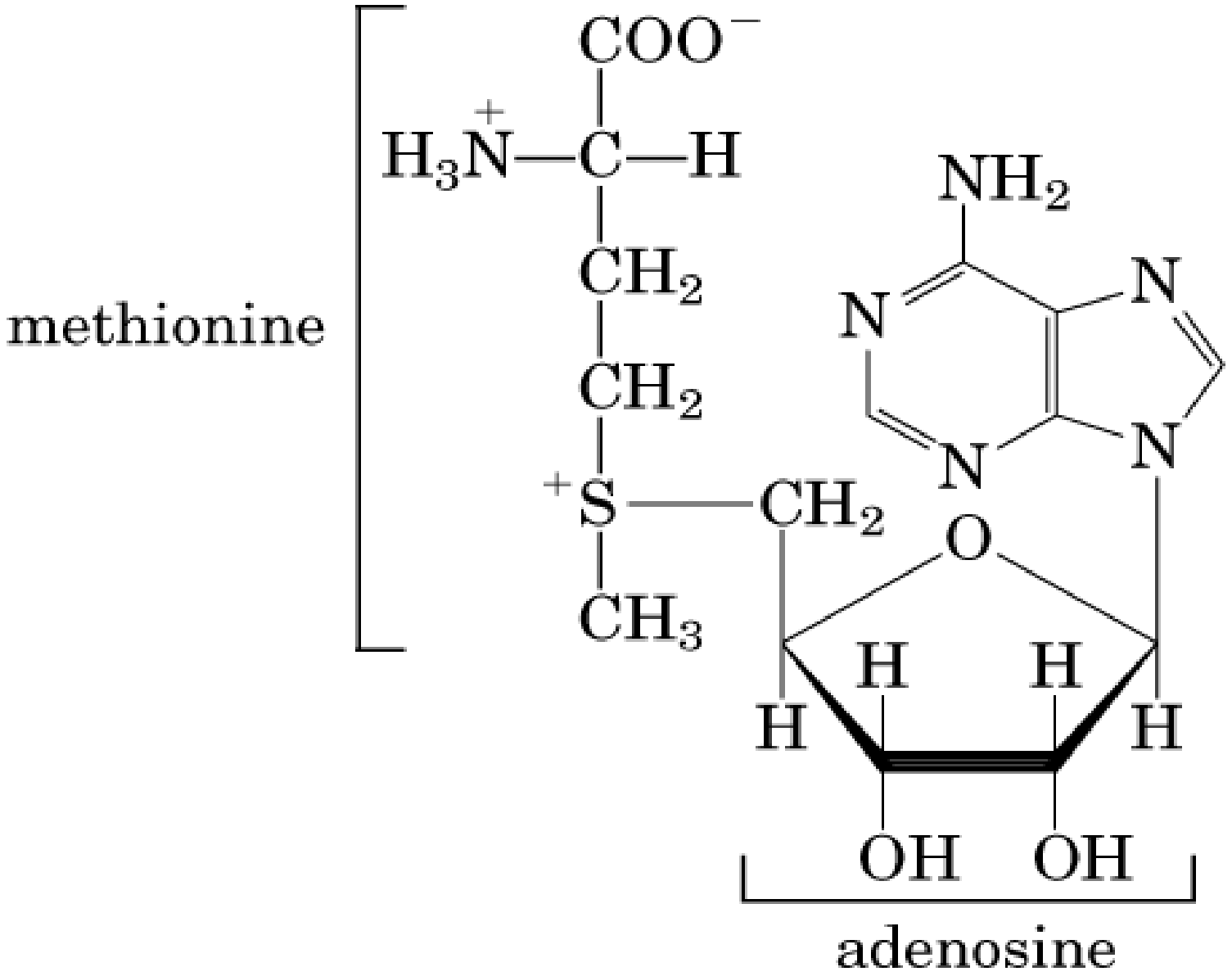
Tetrahydrofolate (H_4 folate)



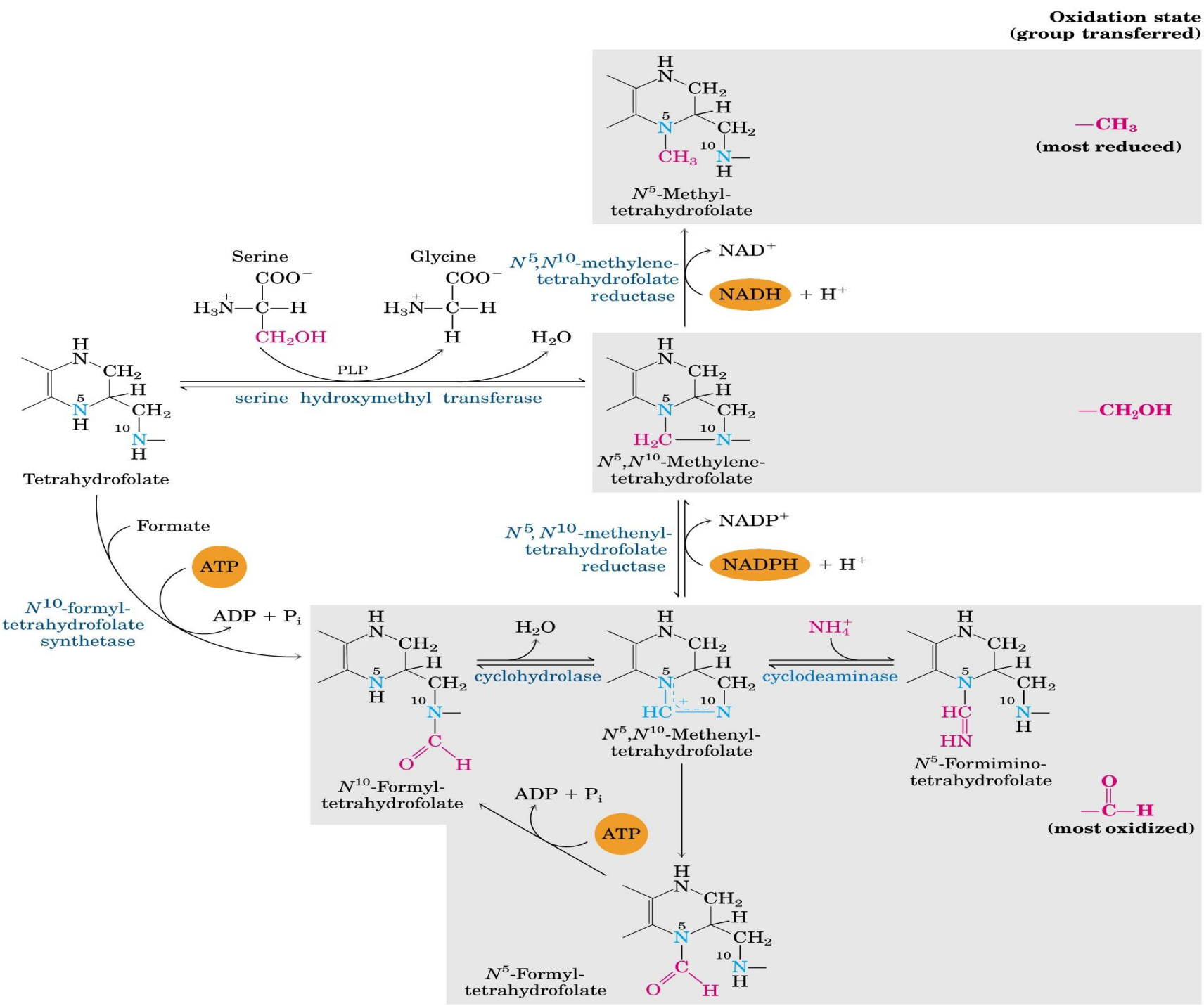
Biotin

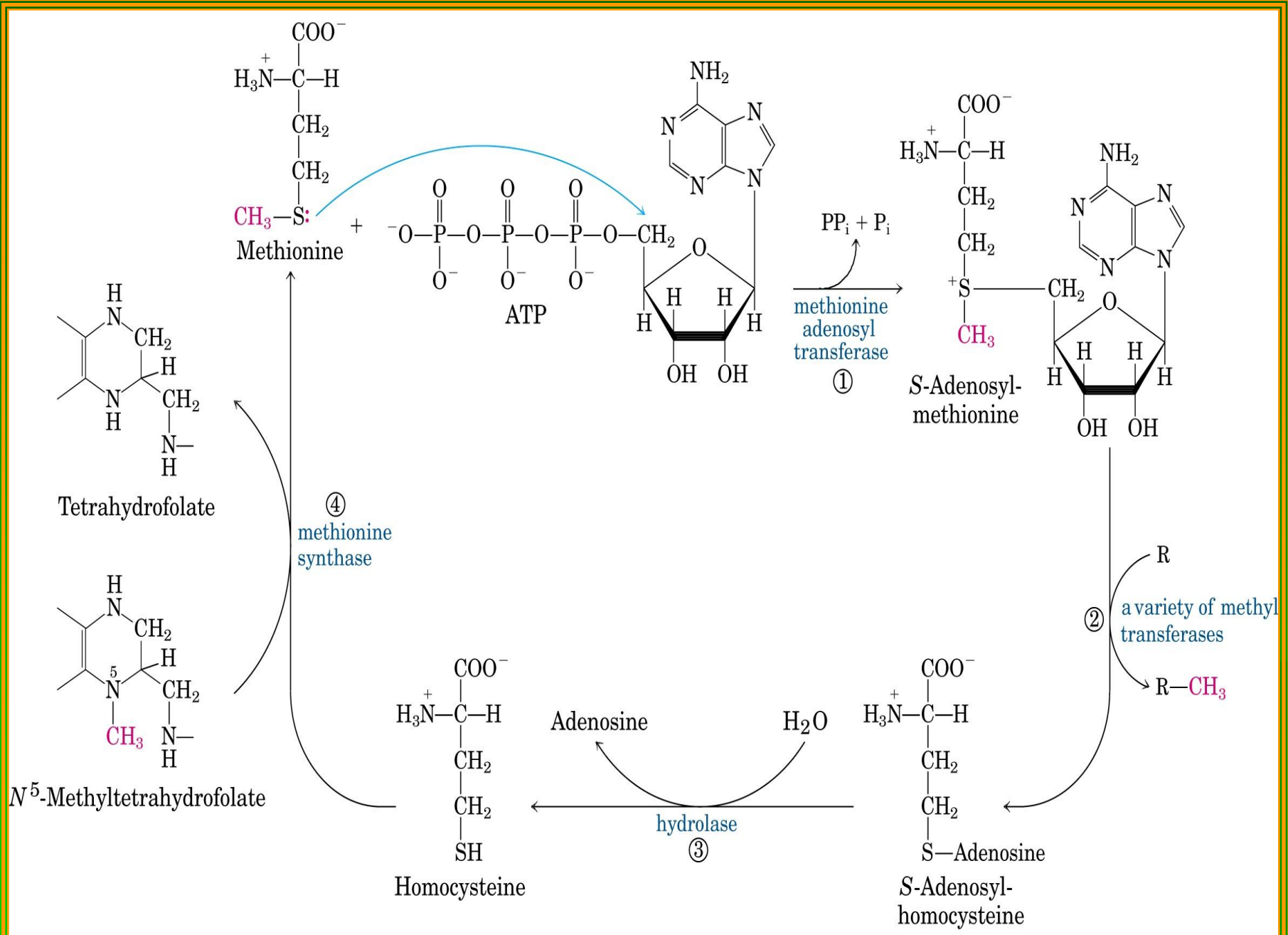


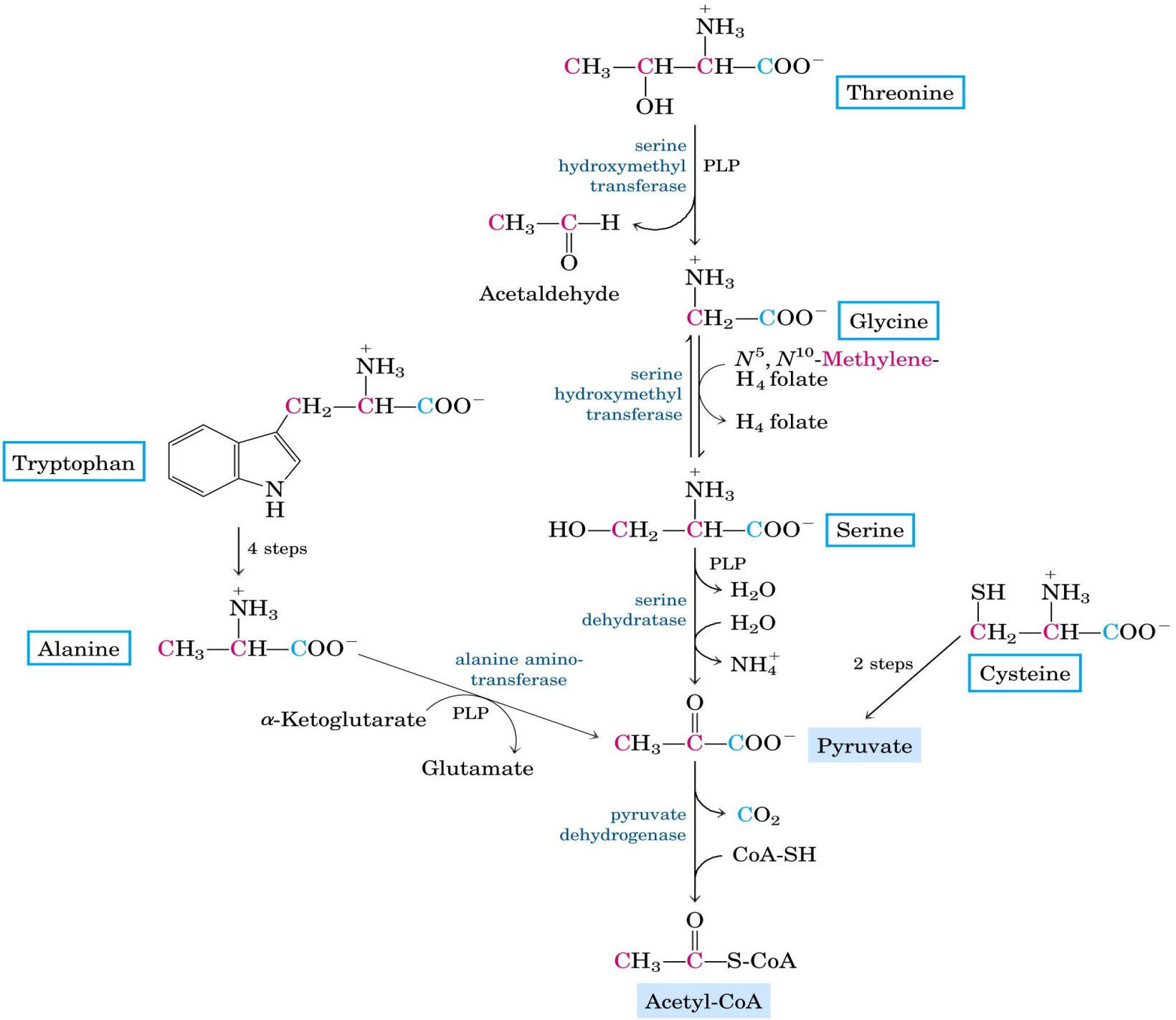
Tetrahydrofolate (H_4 folate)



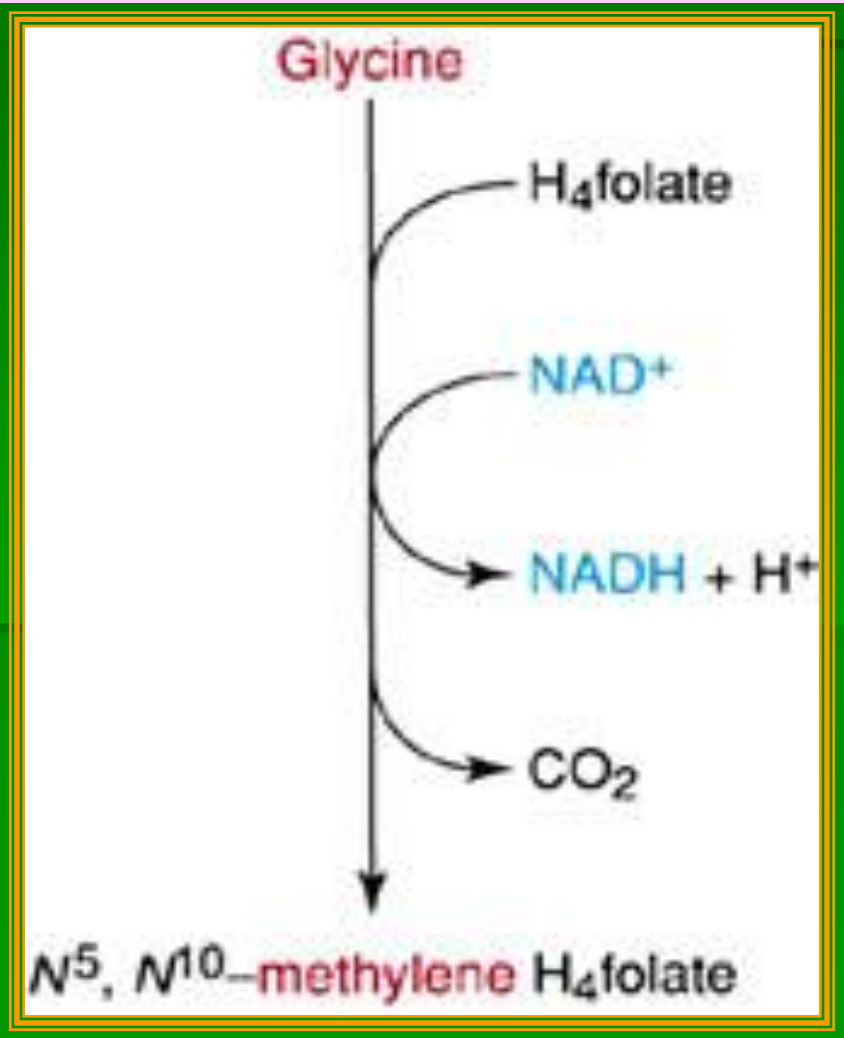
S-Adenosylmethionine (adoMet)

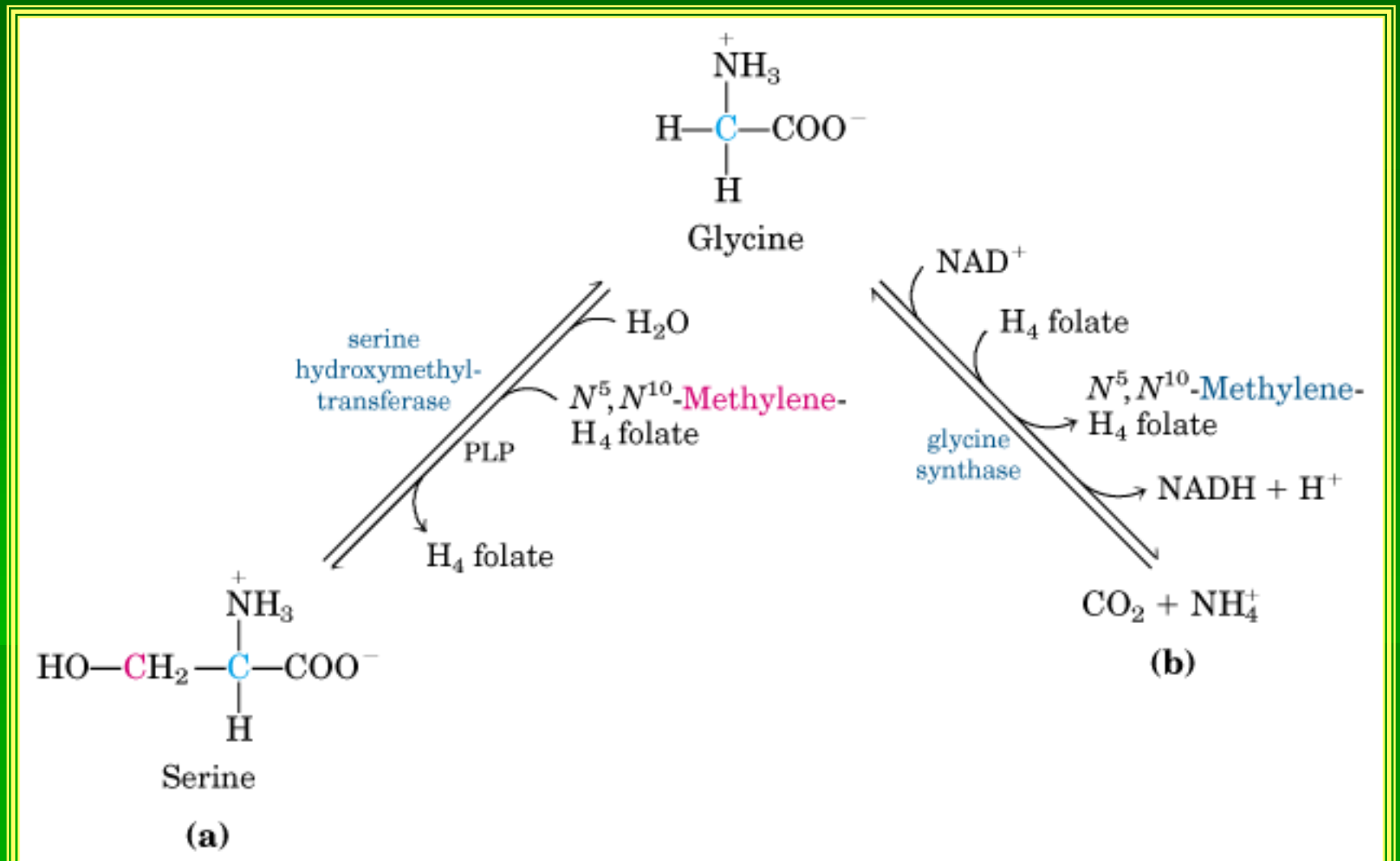

Oxidation state
(group transferred)
N^5-Methyl-
tetrahydrofolate
—CH3
(most reduced)
Serine
Glycine
N^5,N^{10}-methylene-
tetrahydrofolate
reductase
NAD+
NADH
+ H+
PLP
H2O
serine hydroxymethyl transferase
Tetrahydrofolate
N^5,N^{10}-Methylene-
tetrahydrofolate
—CH2OH
Formate
ATP
N^{10}-formyl-
tetrahydrofolate
synthetase
ADP + Pi
N^5, N^{10}-methenyl-
tetrahydrofolate
reductase
NADP+
NADPH
+ H+
H2O
cyclohydrolase
NH4+
cyclodeaminase
N^{10}-Formyl-
tetrahydrofolate
N^5,N^{10}-Methenyl-
tetrahydrofolate
N^5-Formimino-
tetrahydrofolate
—C—H
(most oxidized)
ADP + Pi
ATP
N^5-Formyl-
tetrahydrofolate

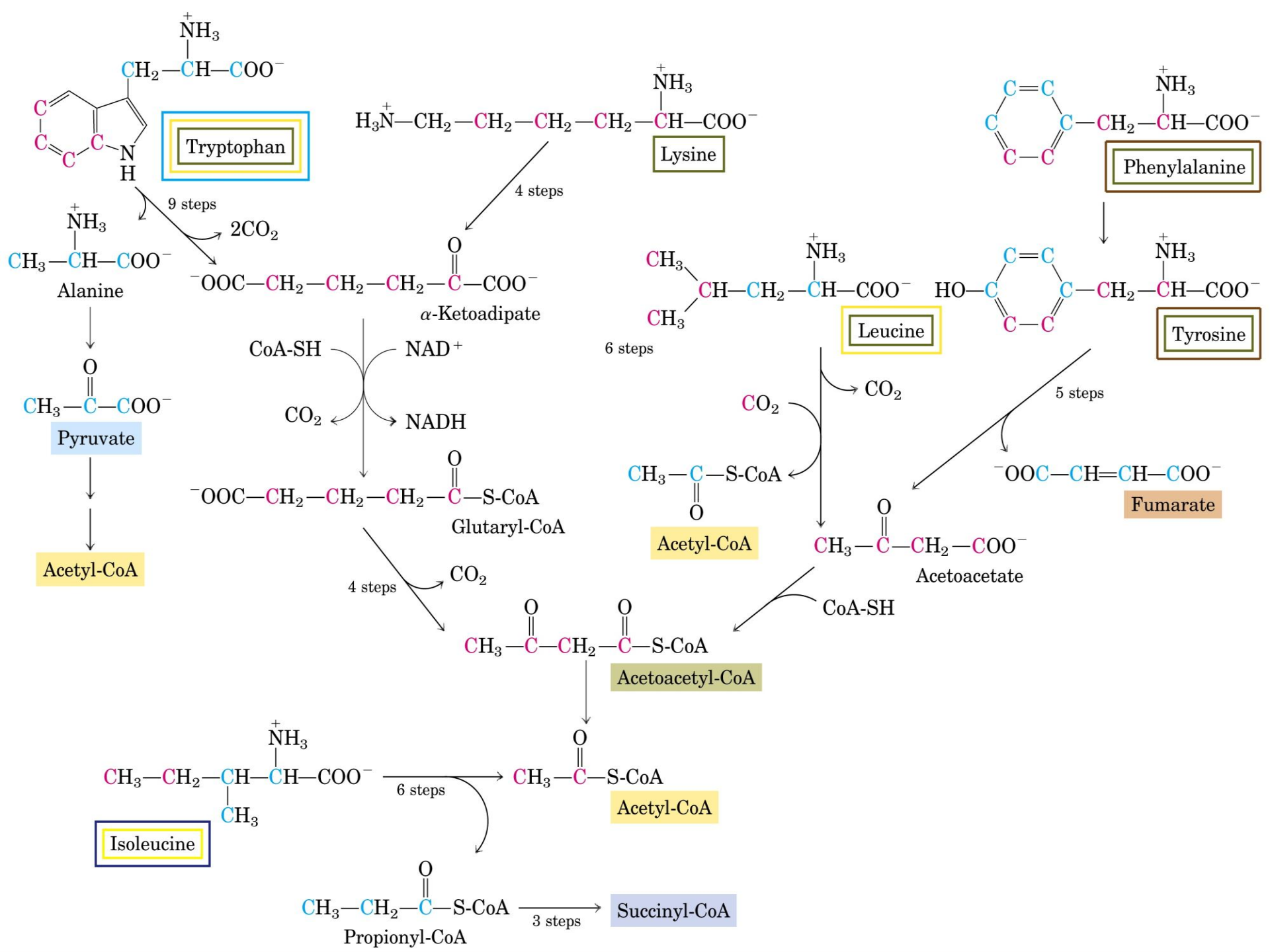

Methionine
ATP
PPi + Pi
methionine adenosyl transferase
①
S-Adenosyl-methionine
②
a variety of methyl transferases
R
R—CH3
S-Adenosyl-homocysteine
S—Adenosine
hydrolase
③
Adenosine
H2O
Homocysteine
④
methionine synthase
Tetrahydrofolate
N5-Methyltetrahydrofolate

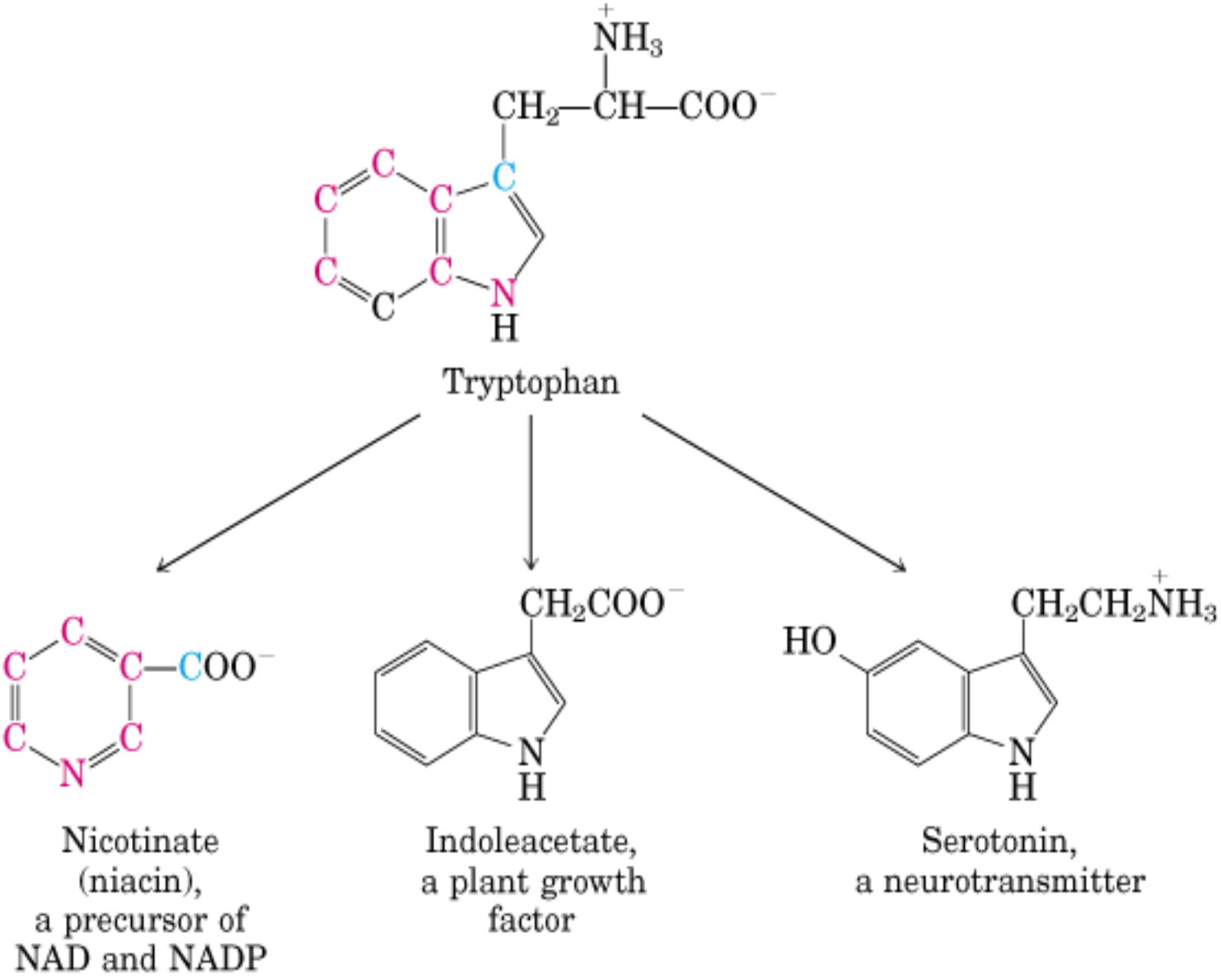

Threonine
serine hydroxymethyl transferase
PLP
Acetaldehyde
Glycine
serine hydroxymethyl transferase
N^5, N^{10}-Methylene-H_4 folate
H_4 folate
Tryptophan
4 steps
Serine
PLP
serine dehydratase
H_2O
H_2O
NH_4^+
Alanine
alanine amino-transferase
PLP
α-Ketoglutarate
Glutamate
2 steps
Cysteine
Pyruvate
pyruvate dehydrogenase
CO_2
CoA-SH
Acetyl-CoA

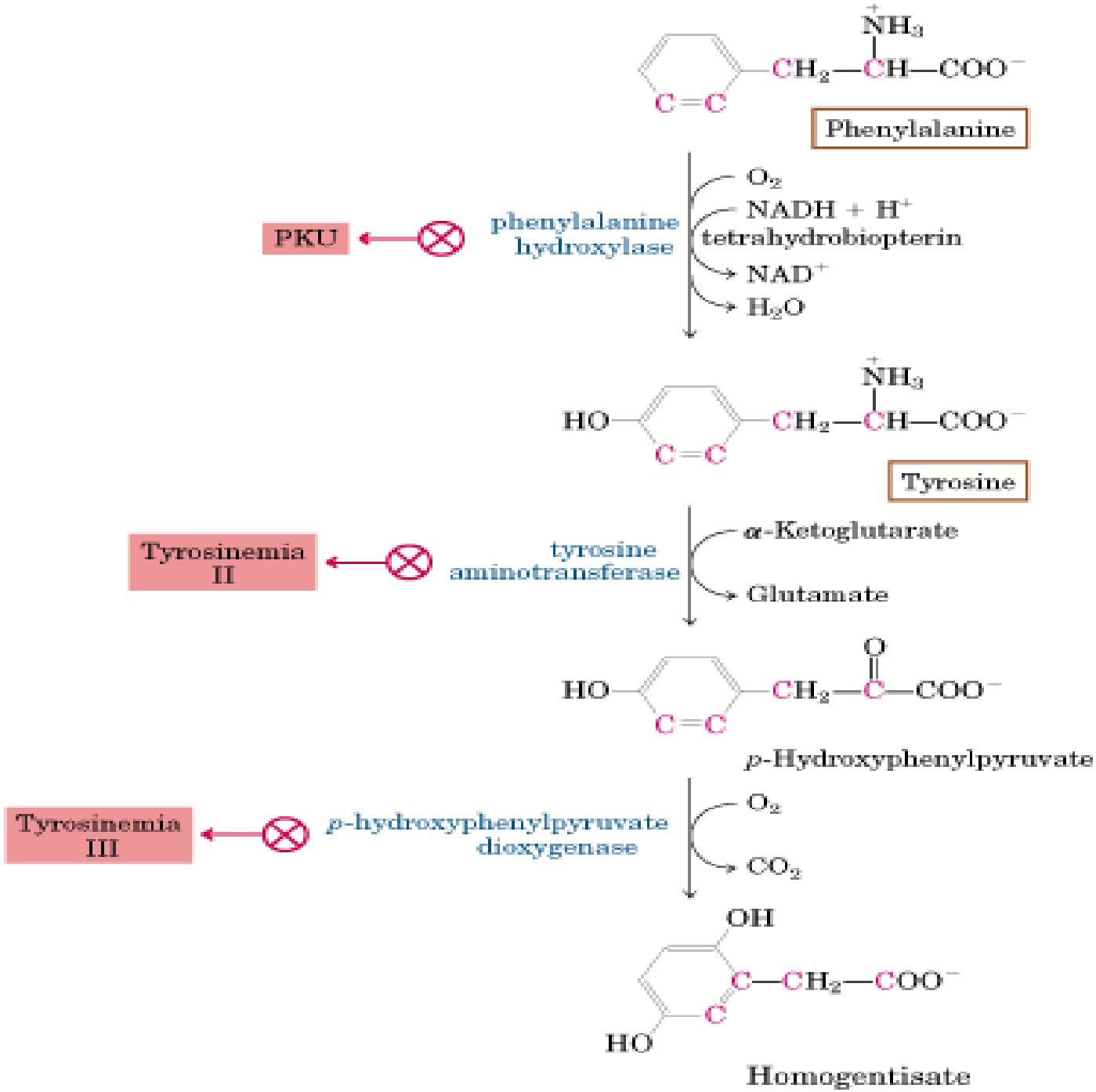
The glycine cleavage complex requires pyridoxal phosphate as cofactor




NH3
H—C—COO⁻
H
Glycine
NAD+
H2O
H4 folate
serine hydroxymethyl-transferase
N5,N10-Methylene-H4 folate
PLP
glycine synthase
N5,N10-Methylene-H4 folate
NADH + H+
H4 folate
CO2 + NH4+
(b)
NH3
HO—CH2—C—COO⁻
H
Serine
(a)


Tryptophan
Lysine
Phenylalanine
9 steps
2CO2
4 steps
Alanine
α-Ketoadipate
Leucine
6 steps
Tyrosine
5 steps
CoA-SH
NAD+
CO2
NADH
CO2
CO2
Pyruvate
Glutaryl-CoA
Acetyl-CoA
Fumarate
Acetyl-CoA
Acetoacetate
4 steps
CO2
CoA-SH
Acetoacetyl-CoA
Isoleucine
6 steps
Acetyl-CoA
3 steps
Propionyl-CoA
Succinyl-CoA


NH3
CH2—CH—COO⁻
Tryptophan
CH2COO⁻
CH2CH2NH3
HO
Nicotinate (niacin), a precursor of NAD and NADP
Indoleacetate, a plant growth factor
Serotonin, a neurotransmitter


Phenylalanine
PKU
phenylalanine hydroxylase
O2
NADH + H+
tetrahydrobiopterin
NAD+
H2O
Tyrosine
Tyrosinemia II
tyrosine aminotransferase
α-Ketoglutarate
Glutamate
p-Hydroxyphenylpyruvate
Tyrosinemia III
p-hydroxyphenylpyruvate dioxygenase
O2
CO2
Homogentisate

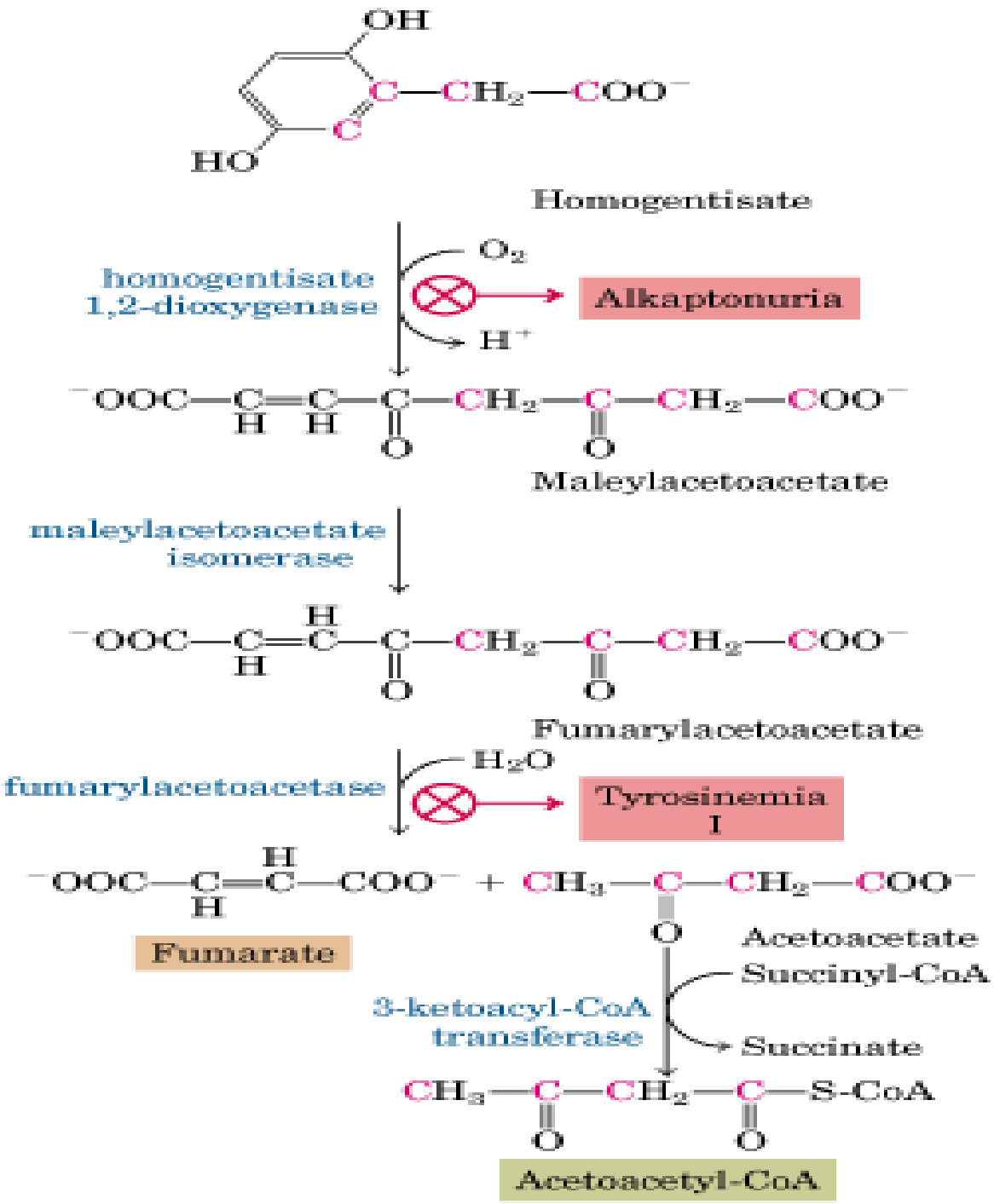
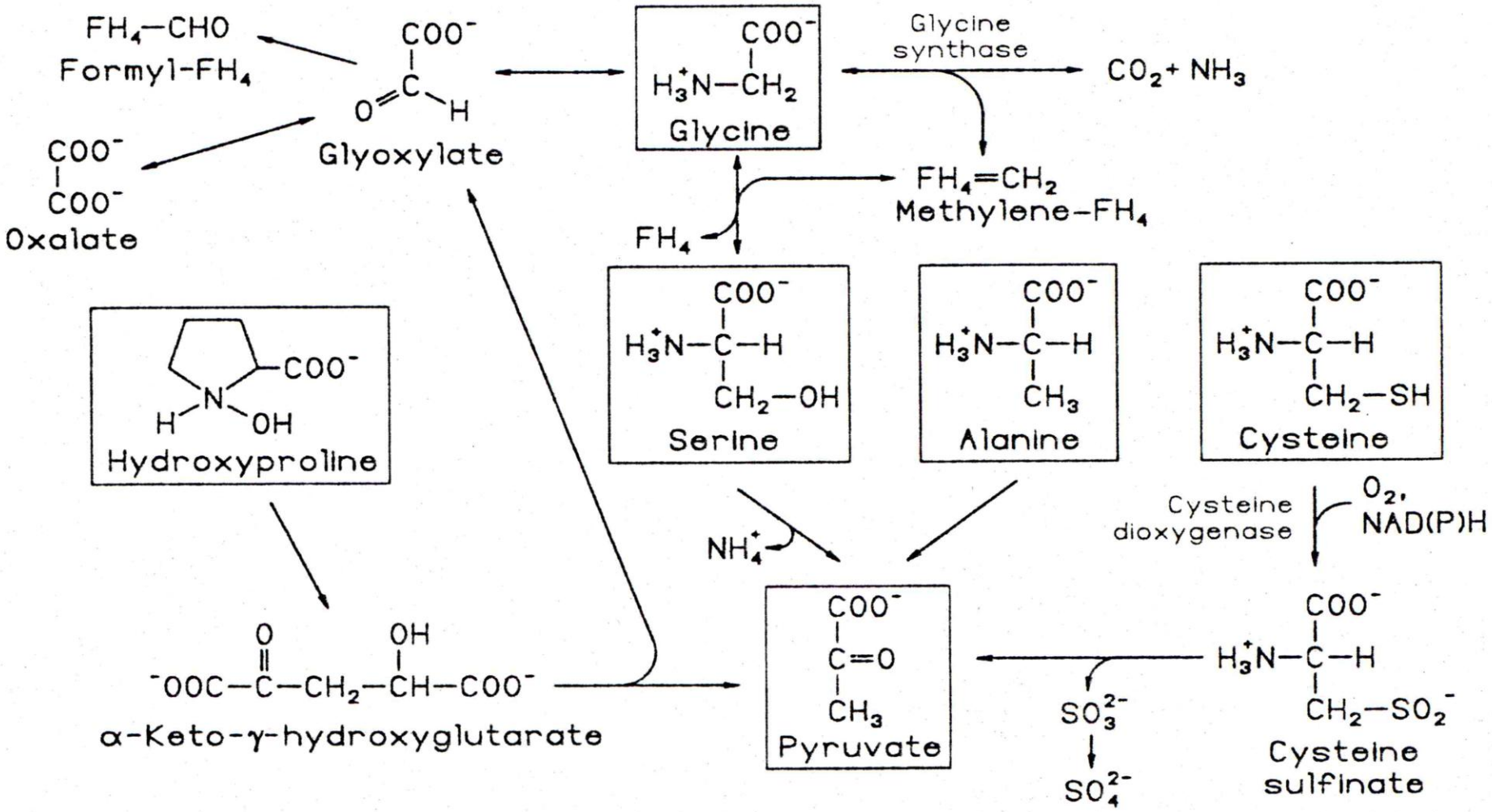

Homogentisate
homogentisate 1,2-dioxygenase
O2
H+
Alkaptonuria
Maleylacetoacetate
maleylacetoacetate isomerase
Fumarylacetoacetate
fumarylacetoacetase
H2O
Tyrosinemia I
Fumarate
Acetoacetate
Succinyl-CoA
3-ketoacyl-CoA transferase
Succinate
Acetoacetyl-CoA

table 18–2

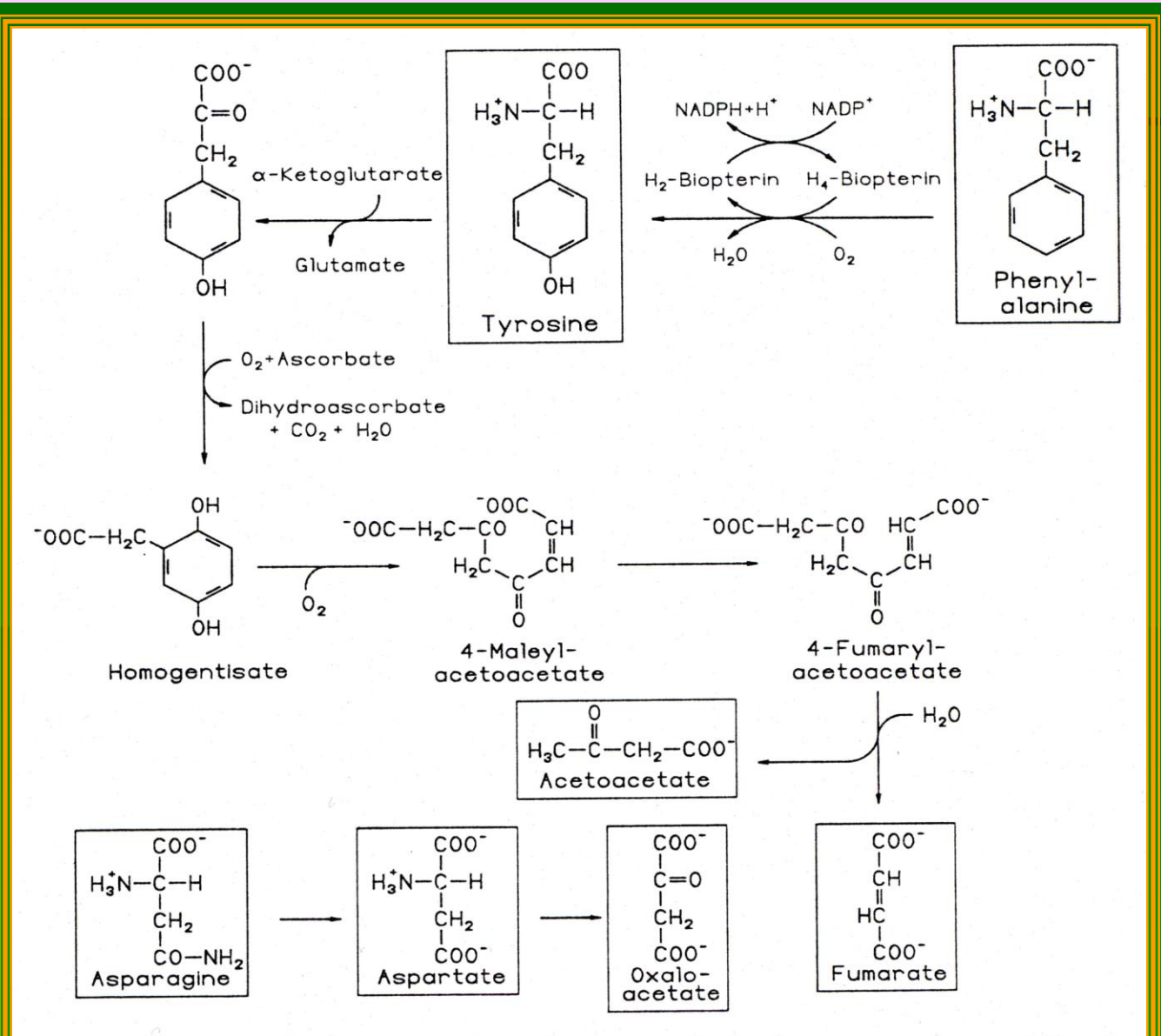
Some Human Genetic Disorders Affecting Amino Acid Catabolism

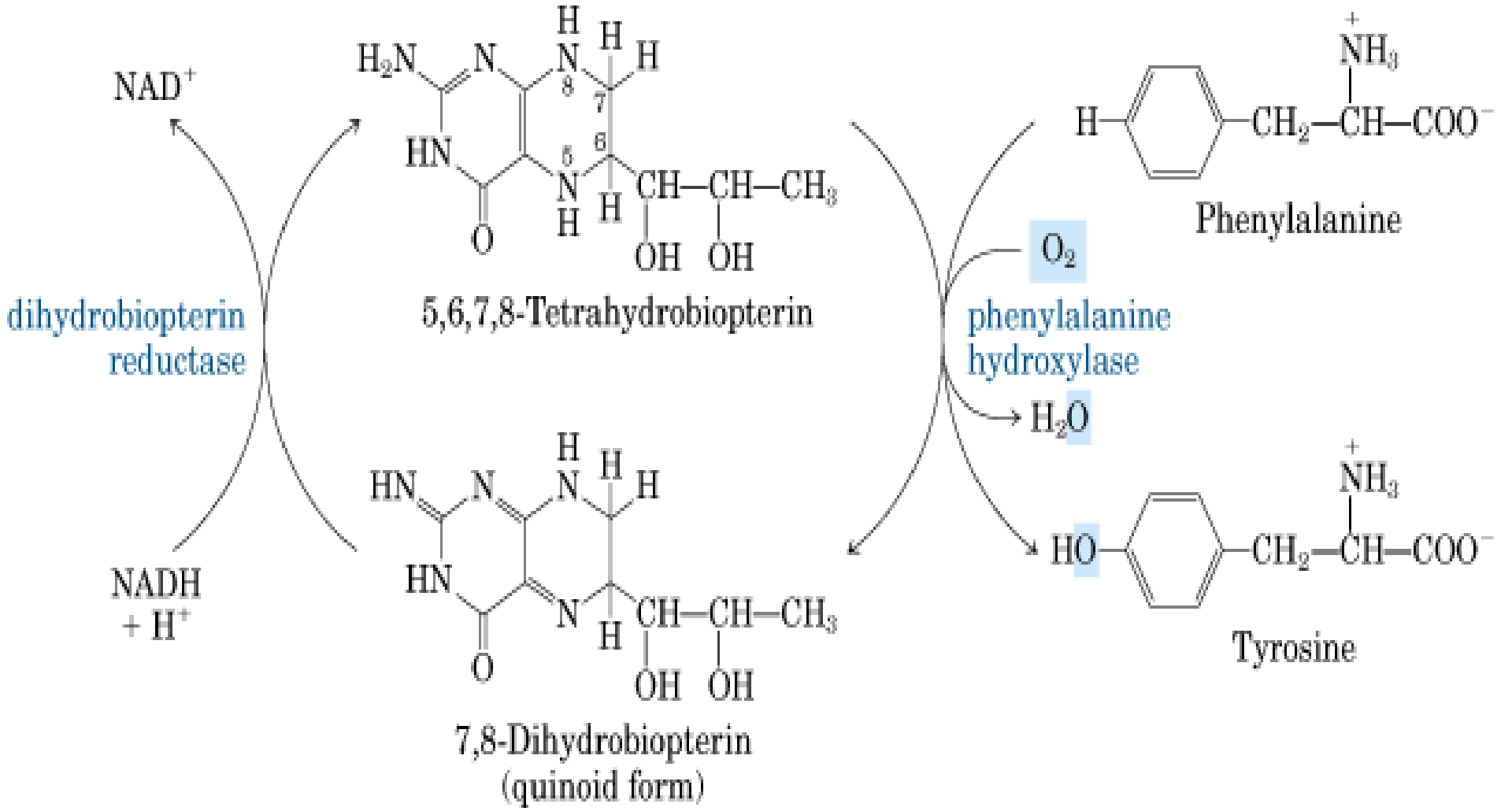
Medical condition	Approximate incidence (per 100,000 births)	Defective process	Defective enzyme	Symptoms and effects
Albinism	3	Melanin synthesis from tyrosine	Tyrosine 3-mono-oxygenase (tyrosinase)	Lack of pigmentation; white hair, pink skin
Alkaptonuria	0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	1.5	Urea synthesis	Argininosuccinate lyase	Vomiting, convulsions
Carbamoyl phosphate synthetase I deficiency	>0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy, convulsions, early death
Homocystinuria	0.5	Methionine degradation	Cystathionine β-synthase	Faulty bone development, mental retardation
Maple syrup urine disease (branched-chain ketoaciduria)	0.4	Isoleucine, leucine, and valine degradation	Branched-chain α-keto acid dehydrogenase complex	Vomiting, convulsions, mental retardation, early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting, convulsions, mental retardation, early death
Phenylketonuria	8	Conversion of phenyl-alanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation

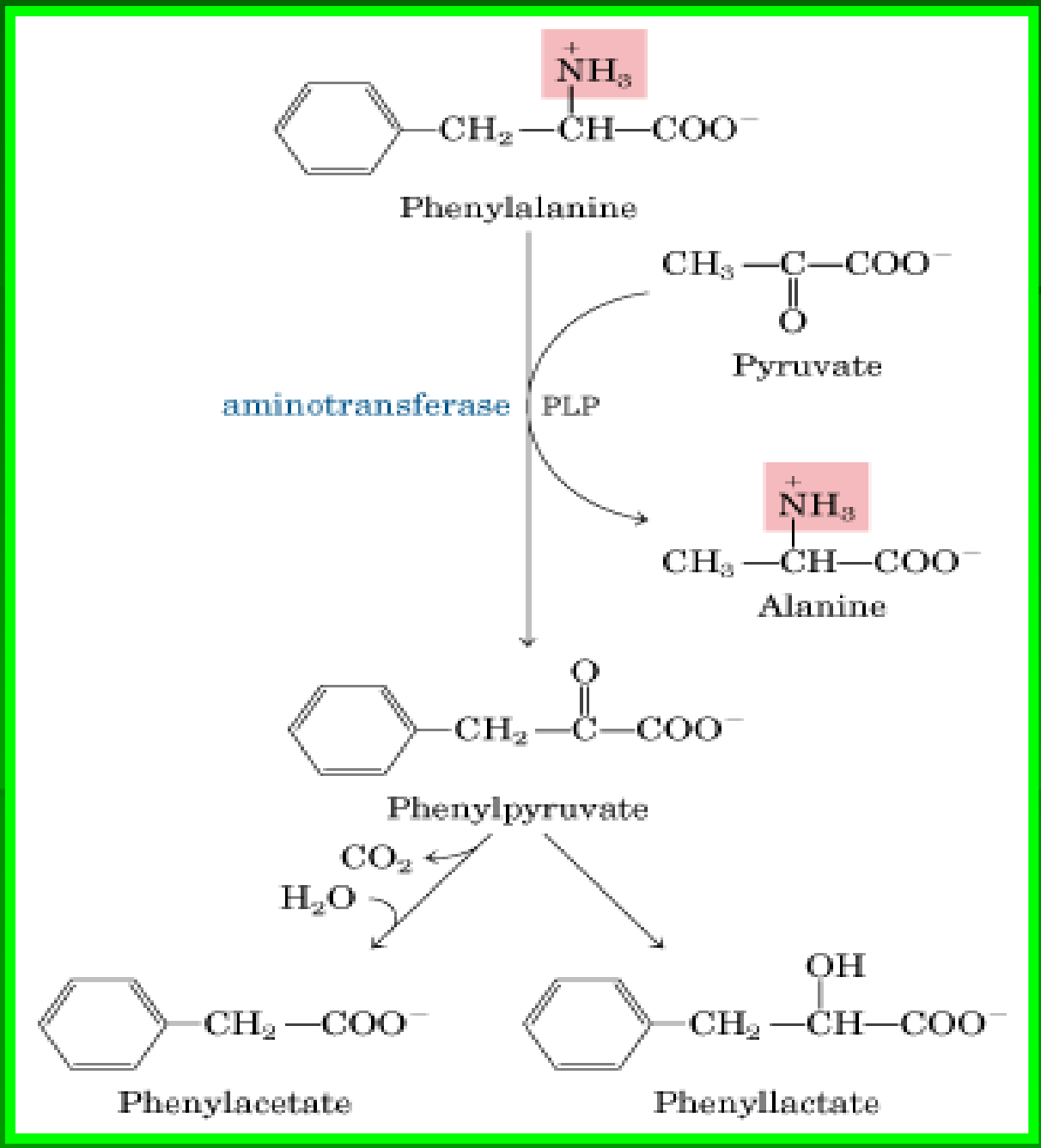
*Amino acid degradation: The pyruvate family



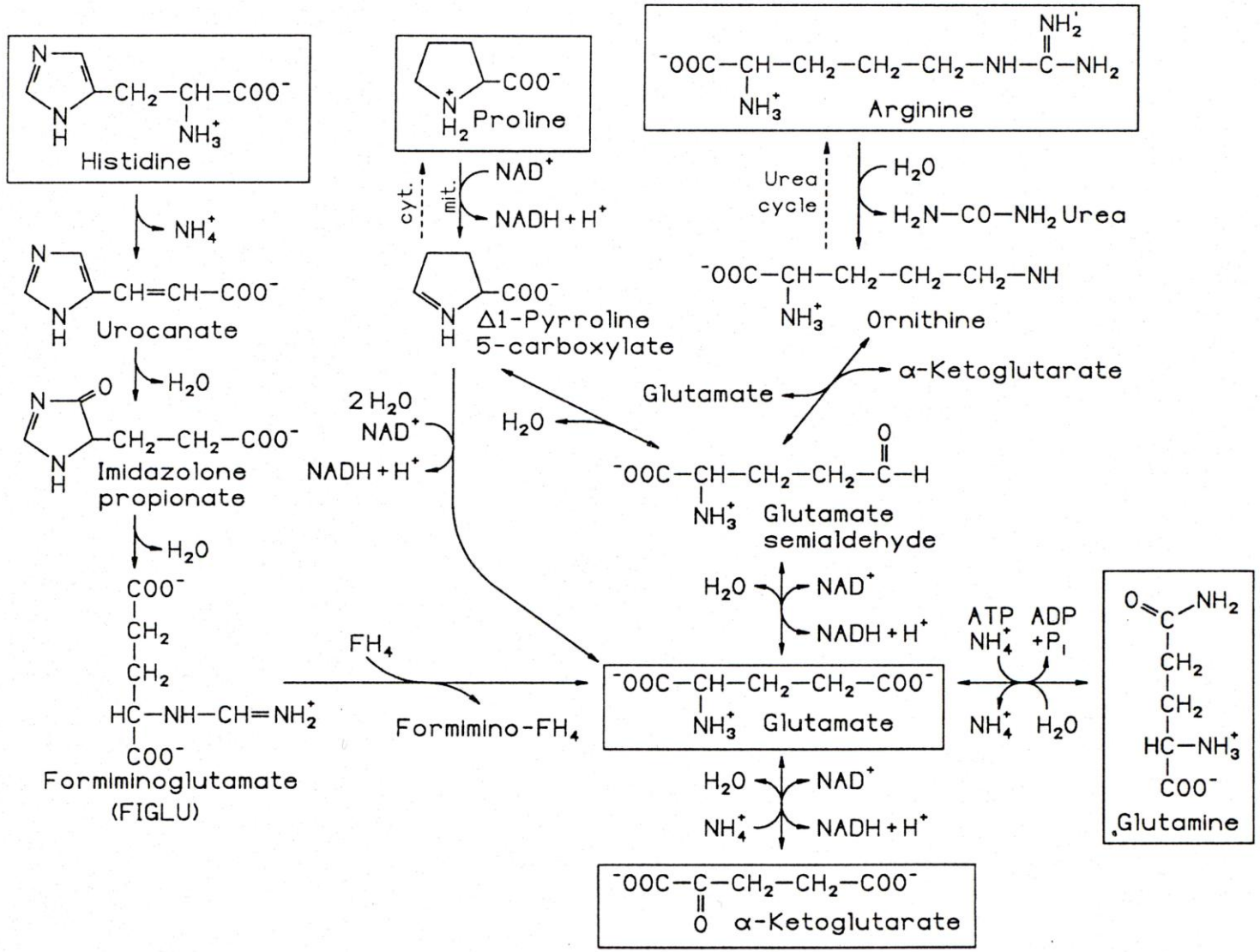
*Amino acid degradation: The fumarate-oxaloacetate family

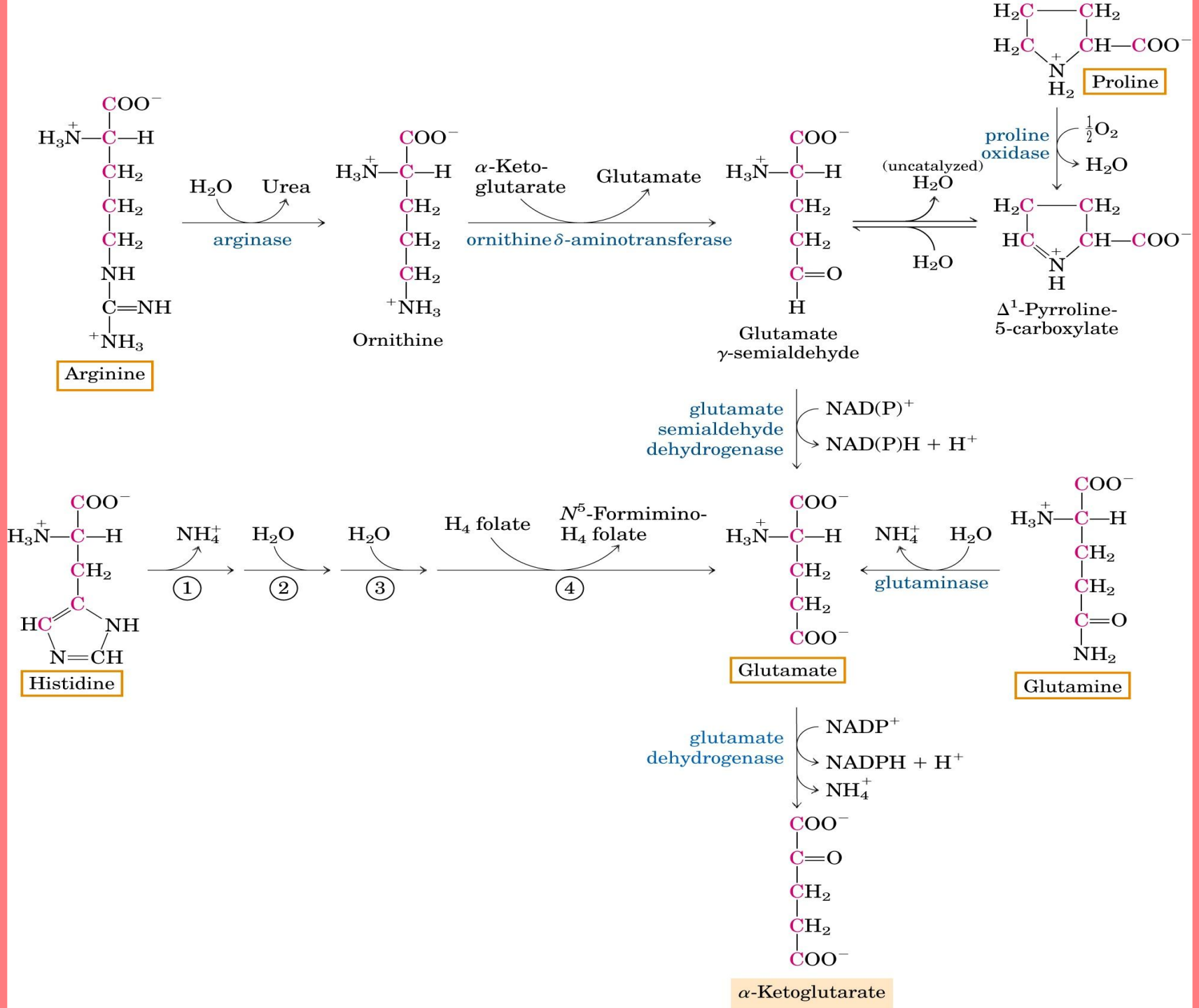



NAD+
NADH
+ H+
dihydrobiopterin
reductase
5,6,7,8-Tetrahydrobiopterin
7,8-Dihydrobiopterin
(quinoid form)
O2
H2O
phenylalanine
hydroxylase
Phenylalanine
Tyrosine

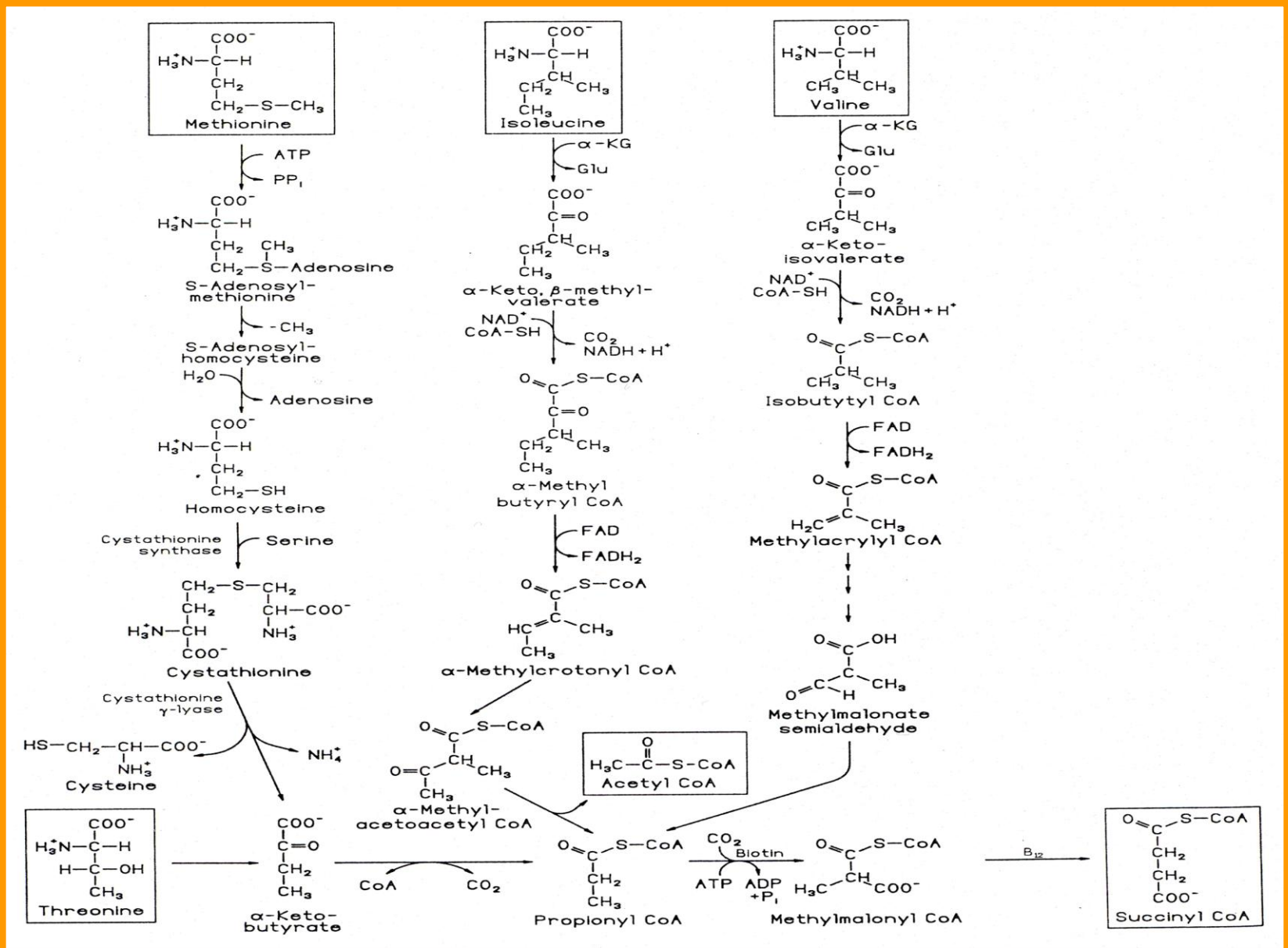

Phenylalanine
Pyruvate
aminotransferase
PLP
Alanine
Phenylpyruvate
Phenylacetate
Phenyllactate

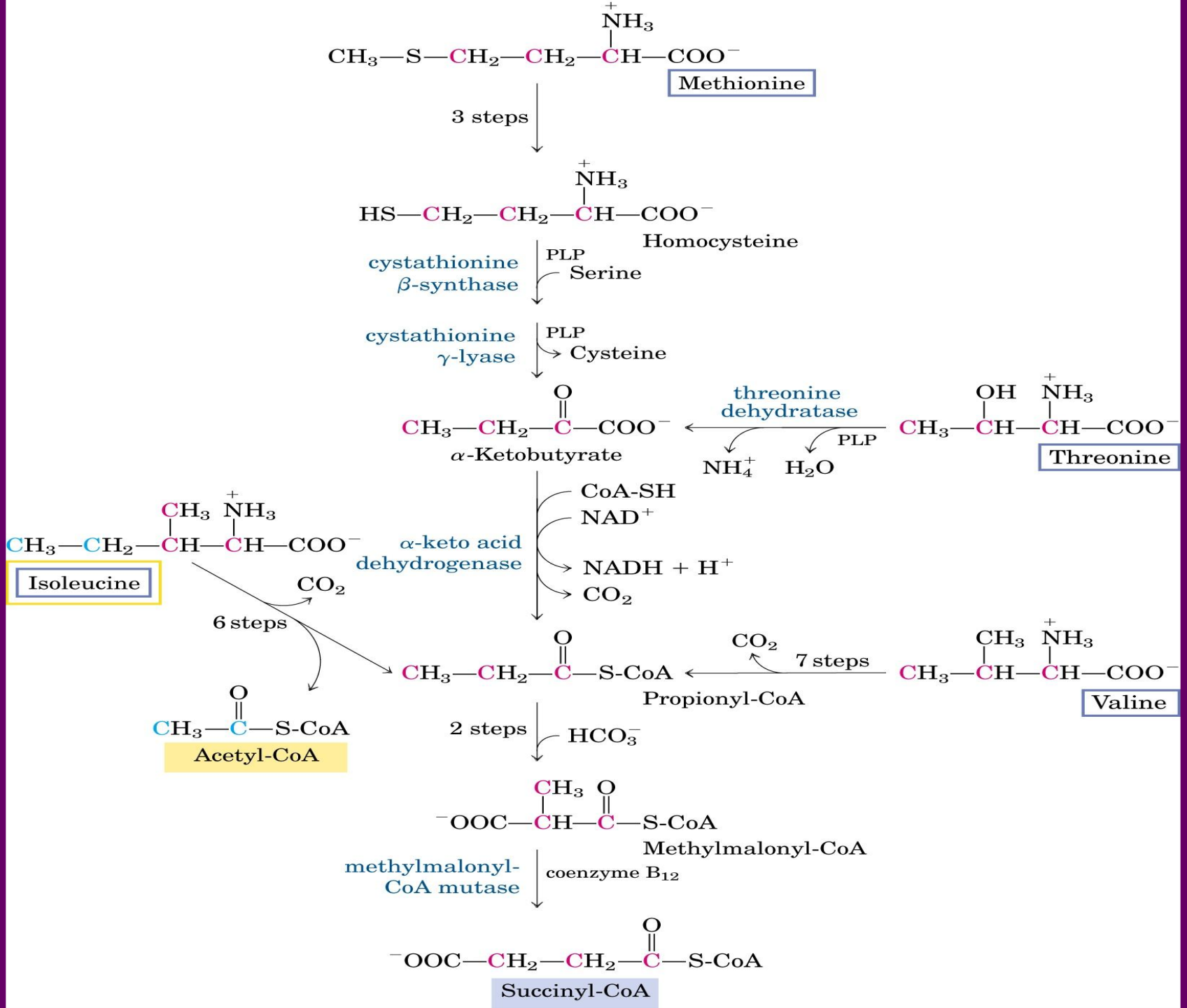
*Amino acid degradation: The a-ketoglutarate family

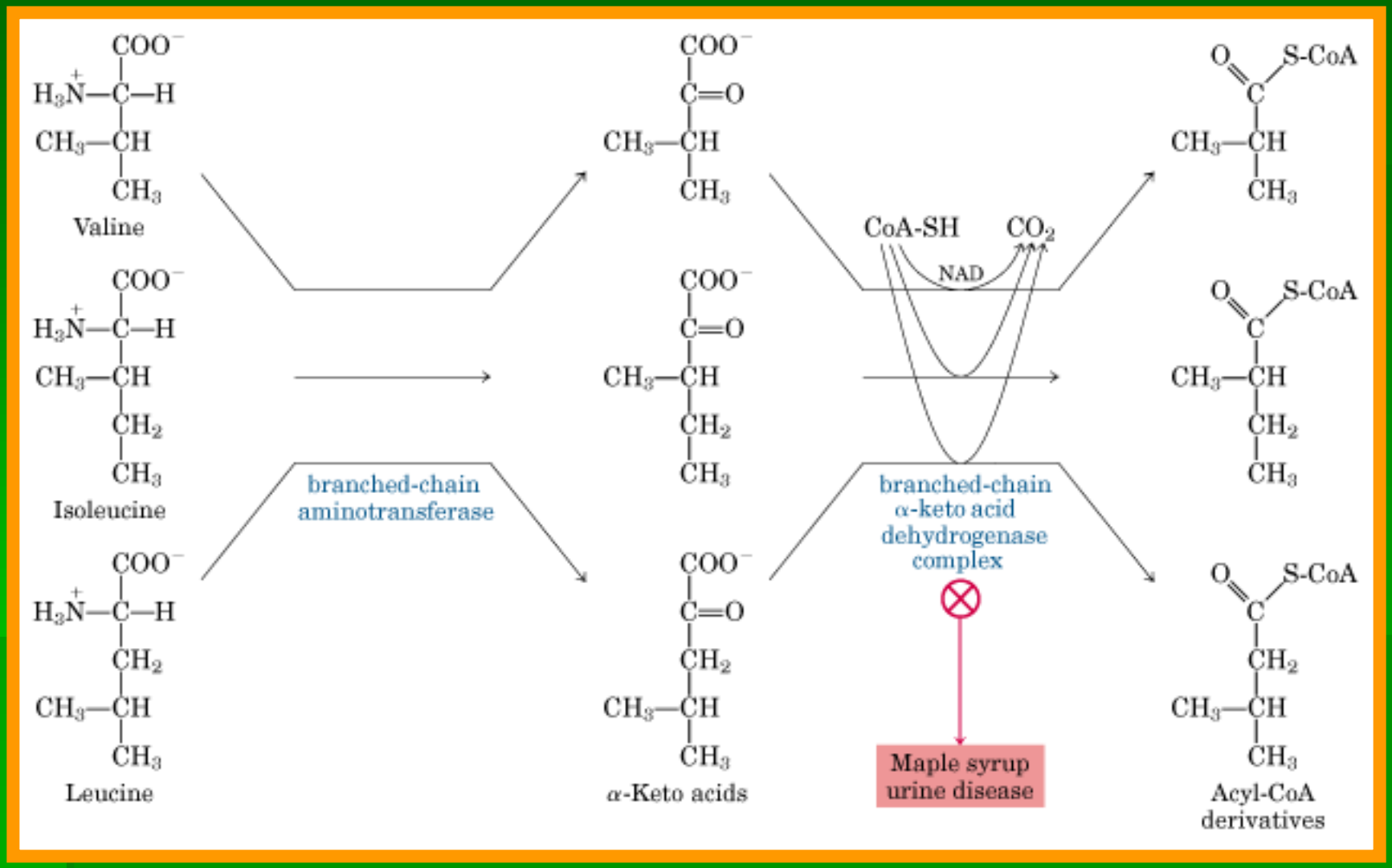


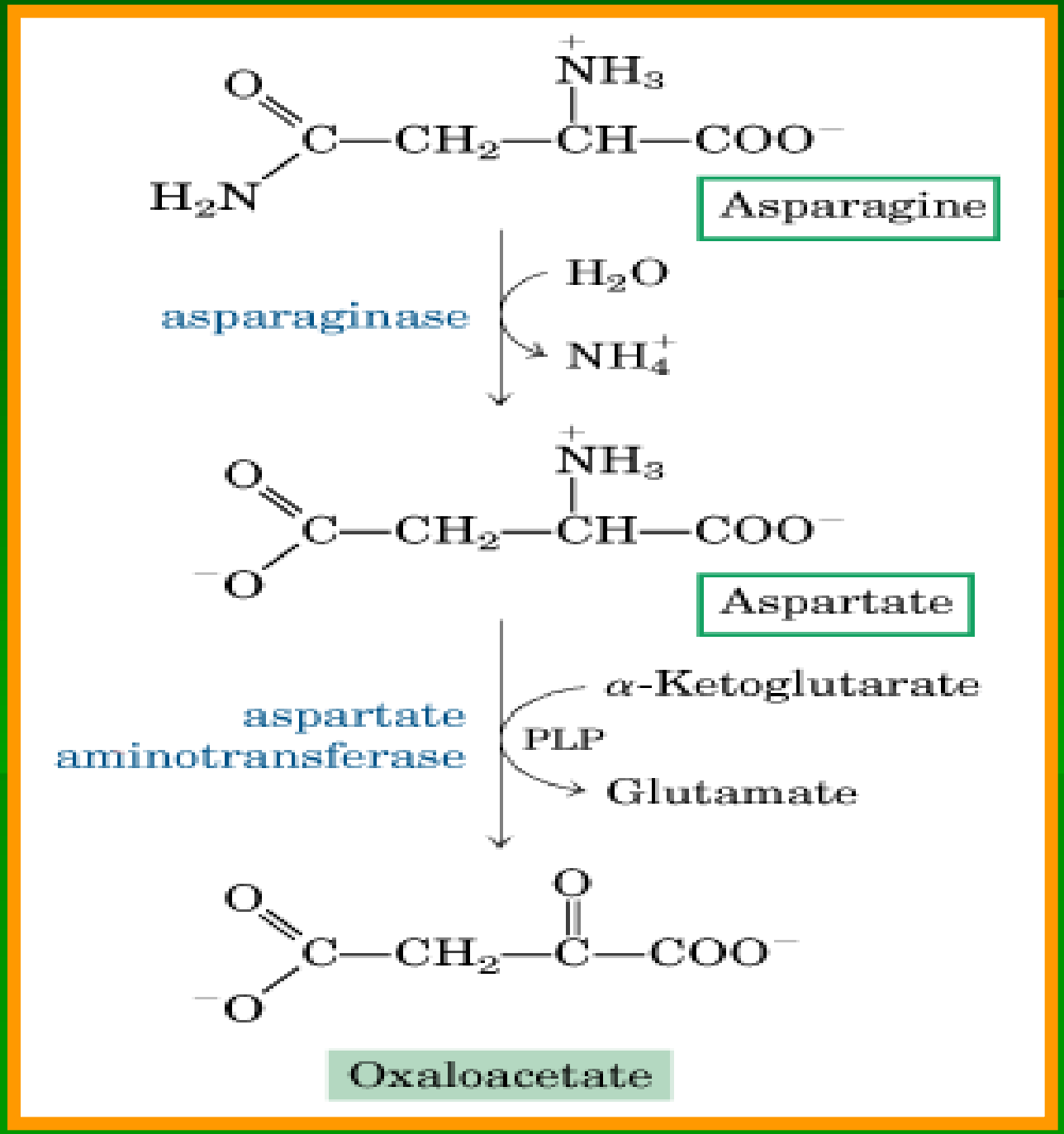

Arginine
H2O
Urea
arginase
Ornithine
α-Keto-glutarate
Glutamate
ornithine δ-aminotransferase
Glutamate γ-semialdehyde
(uncatalyzed)
H2O
H2O
Δ1-Pyrroline-5-carboxylate
proline oxidase
½O2
H2O
Proline
glutamate semialdehyde dehydrogenase
NAD(P)+
NAD(P)H + H+
Histidine
NH4+
H2O
H2O
H4 folate
N5-Formimino-H4 folate
1
2
3
4
Glutamate
NH4+
H2O
glutaminase
Glutamine
glutamate dehydrogenase
NADP+
NADPH + H+
NH4+
α-Ketoglutarate

*Amino acid degradation: The succinyl CoA family

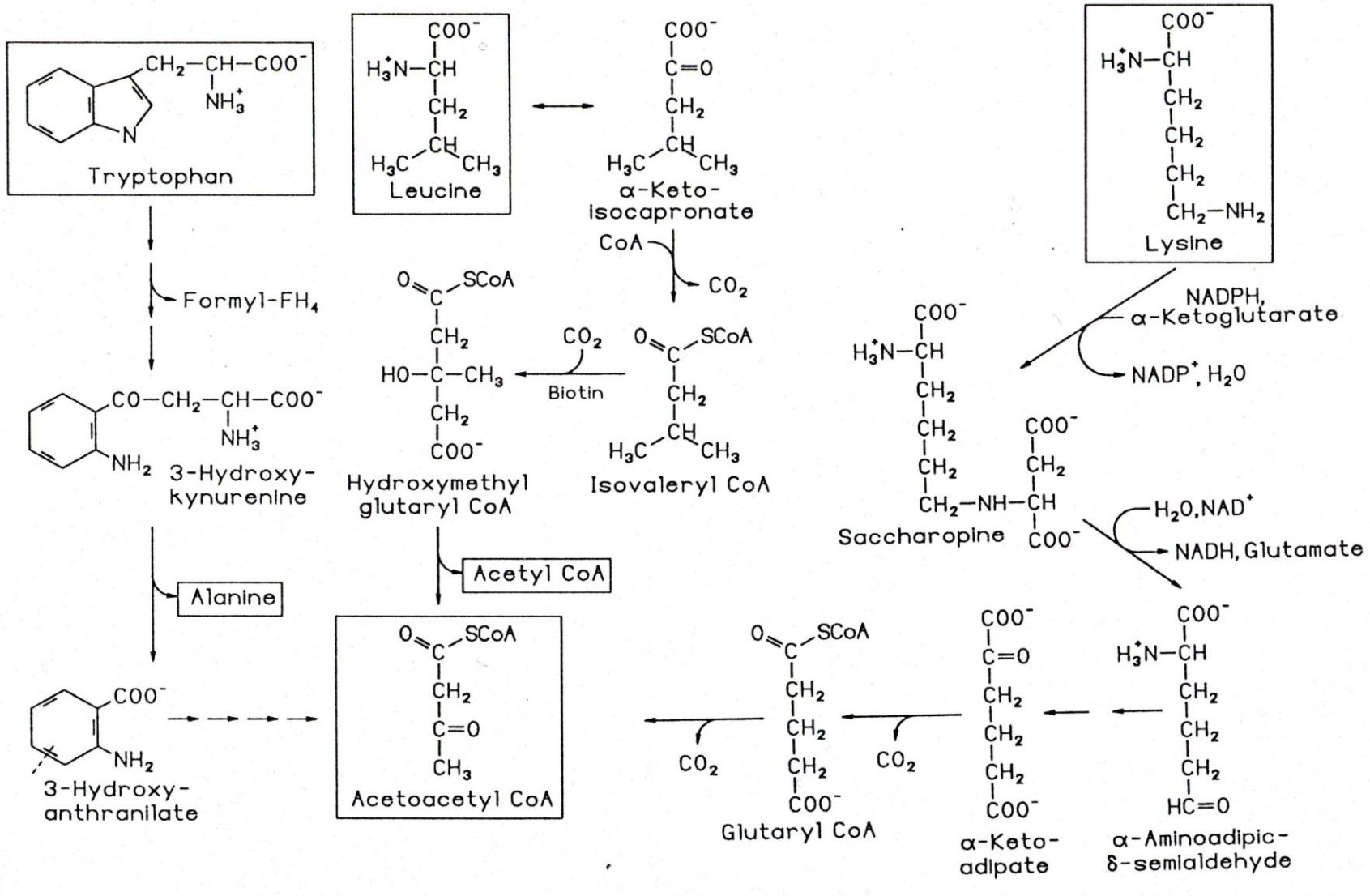


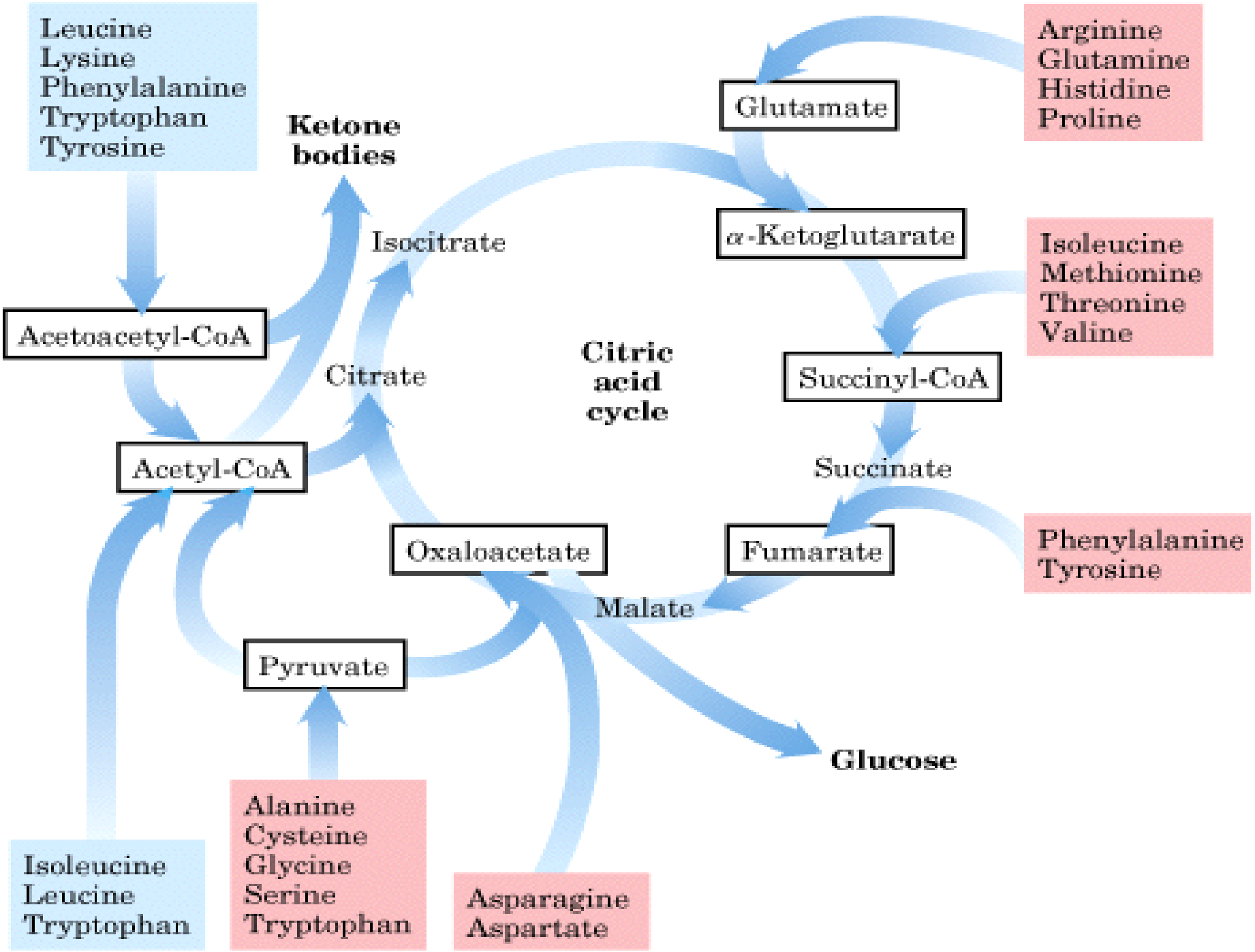

Methionine
3 steps
Homocysteine
cystathionine β-synthase
PLP
Serine
cystathionine γ-lyase
PLP
Cysteine
α-Ketobutyrate
threonine dehydratase
PLP
NH4+
H2O
Threonine
Isoleucine
α-keto acid dehydrogenase
CoA-SH
NAD+
NADH + H+
CO2
6 steps
CO2
7 steps
Propionyl-CoA
Valine
Acetyl-CoA
2 steps
HCO3−
Methylmalonyl-CoA
methylmalonyl-CoA mutase
coenzyme B12
Succinyl-CoA


Valine
Isoleucine
Leucine
branched-chain aminotransferase
α-Keto acids
CoA-SH
CO2
NAD
branched-chain α-keto acid dehydrogenase complex
Maple syrup urine disease
S-CoA
Acyl-CoA derivatives


Asparagine
asparaginase
H_2O
NH_4^+
Aspartate
aspartate aminotransferase
α-Ketoglutarate
PLP
Glutamate
Oxaloacetate

*Amino acid degradation: The acetoacetyl CoA family




Leucine
Lysine
Phenylalanine
Tryptophan
Tyrosine
Ketone bodies
Glutamate
Arginine
Glutamine
Histidine
Proline
Isocitrate
α-Ketoglutarate
Isoleucine
Methionine
Threonine
Valine
Acetoacetyl-CoA
Citrate
Citric acid cycle
Succinyl-CoA
Acetyl-CoA
Succinate
Oxaloacetate
Fumarate
Phenylalanine
Tyrosine
Malate
Pyruvate
Glucose
Alanine
Cysteine
Glycine
Serine
Tryptophan
Isoleucine
Leucine
Tryptophan
Asparagine
Aspartate