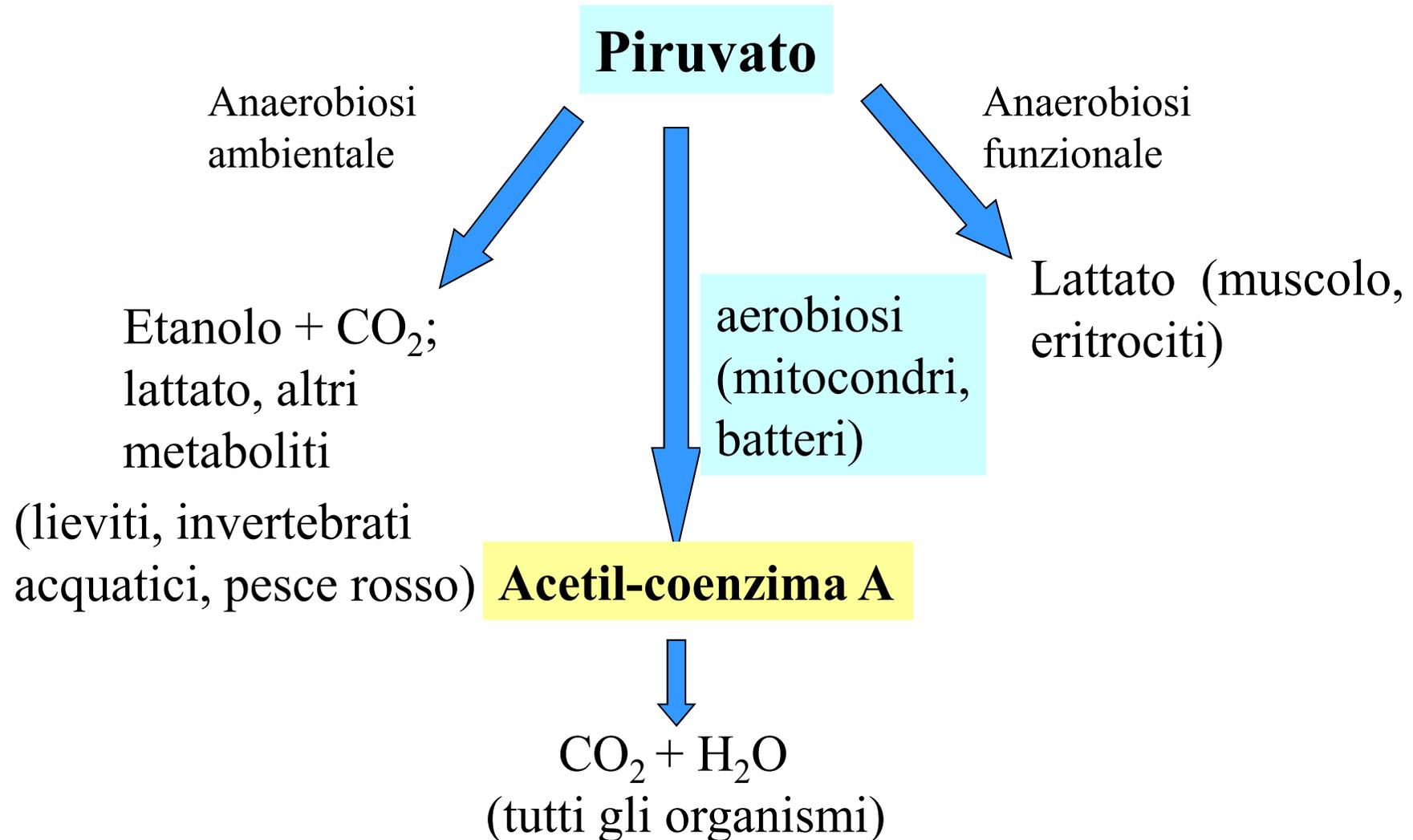
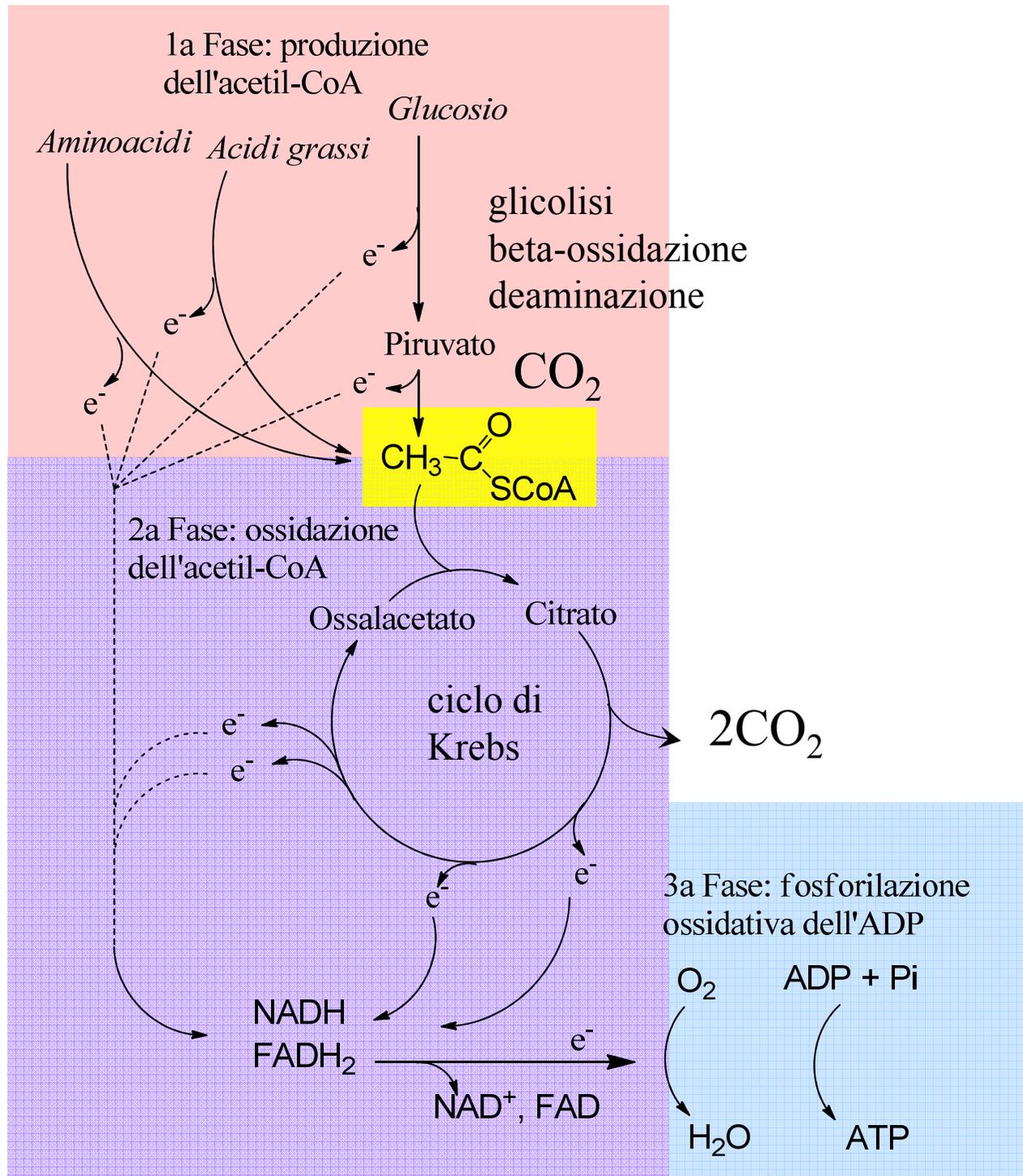
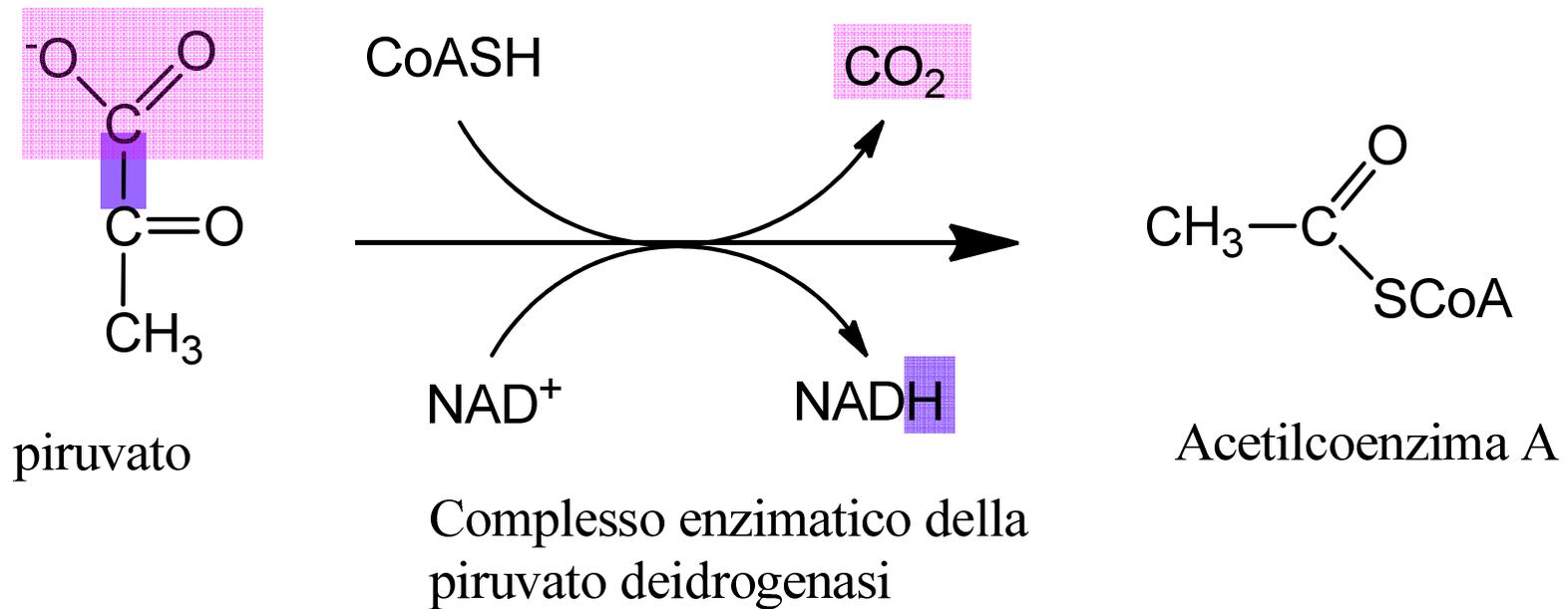


Destini catabolici del piruvato





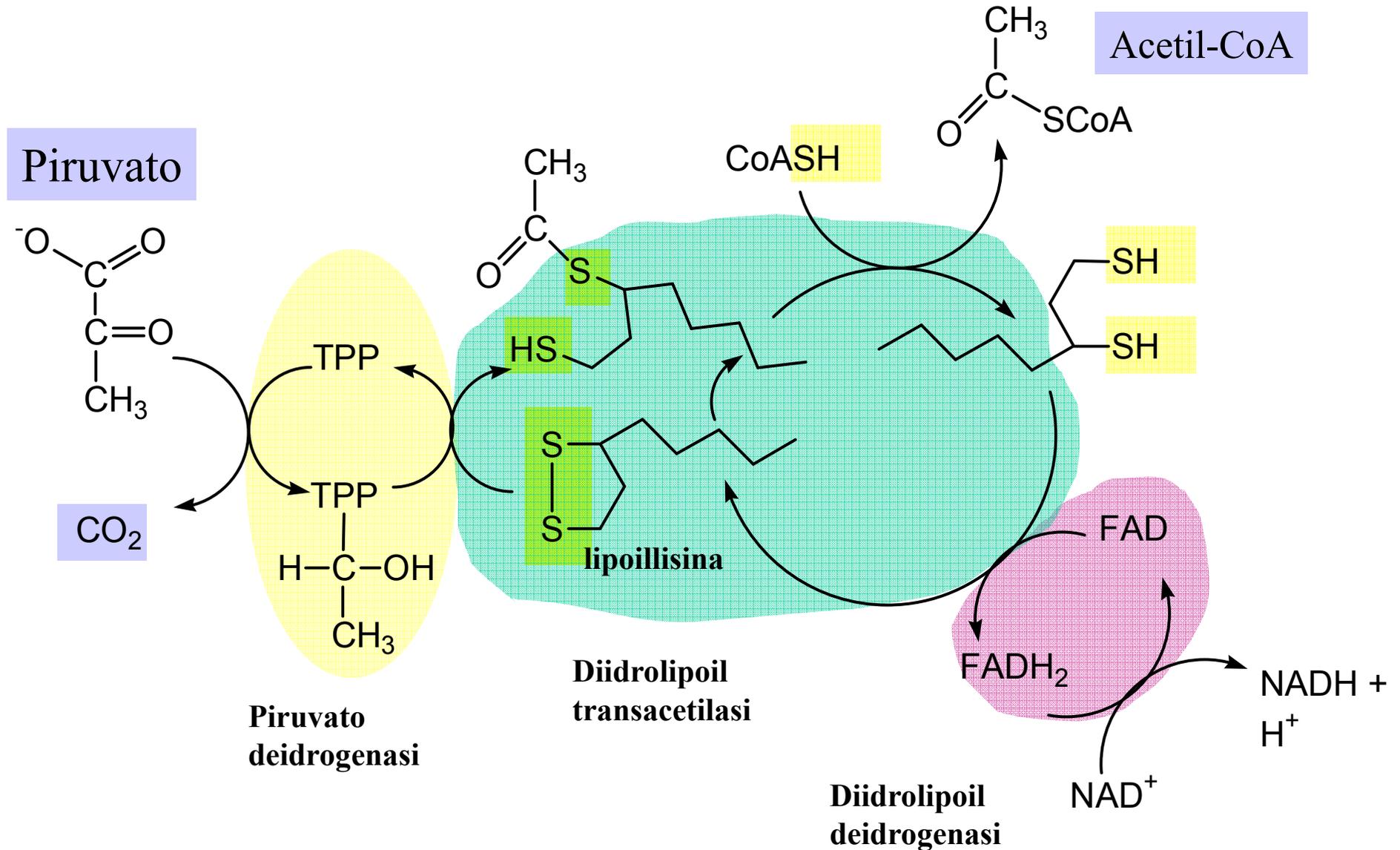
Ossidazione del piruvato: reazione di collegamento tra glicolisi e ciclo di Krebs. Avviene nei mitocondri

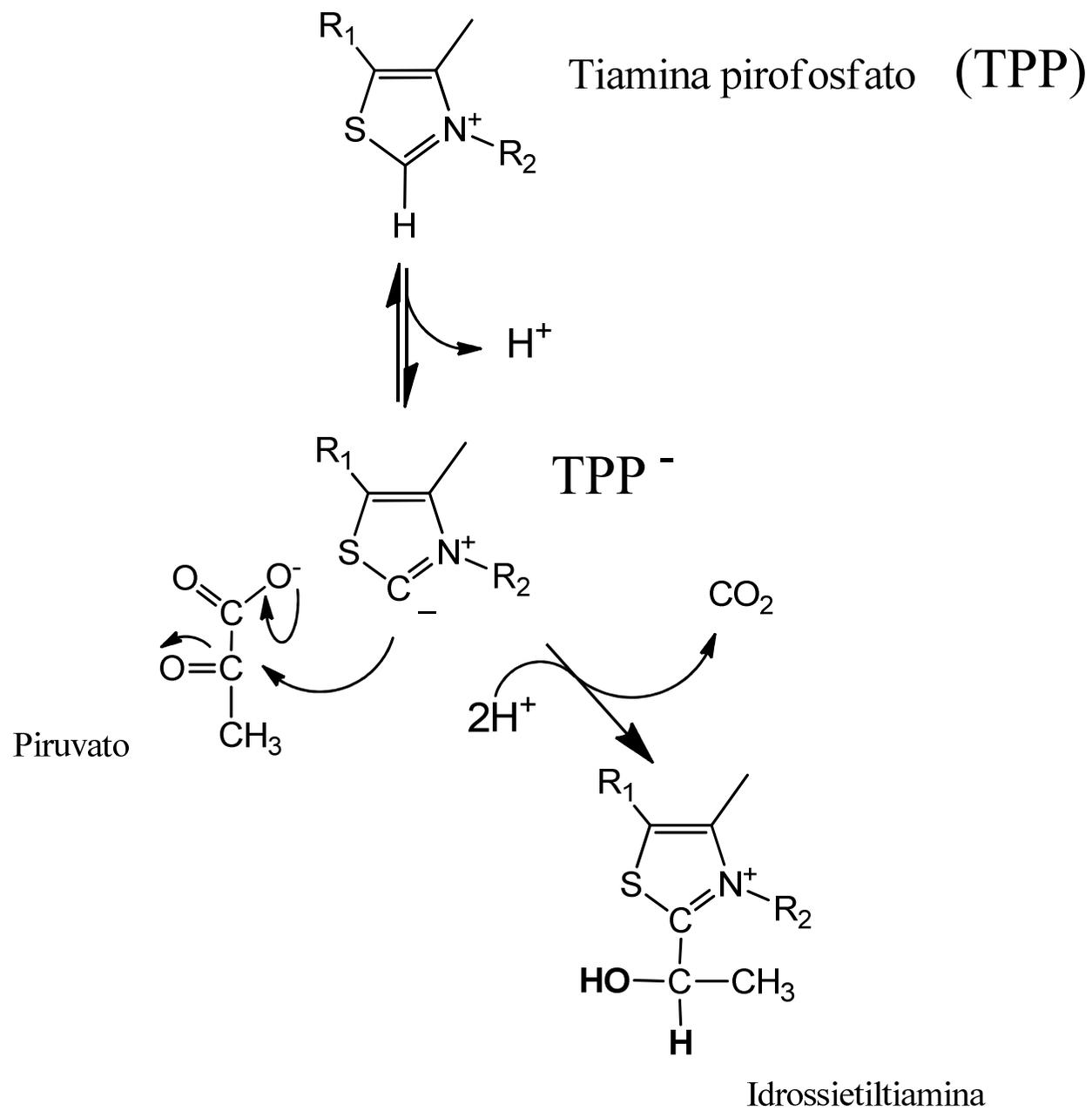


$$\Delta G^{\circ'} = -33.4 \text{ KJ/mol}$$

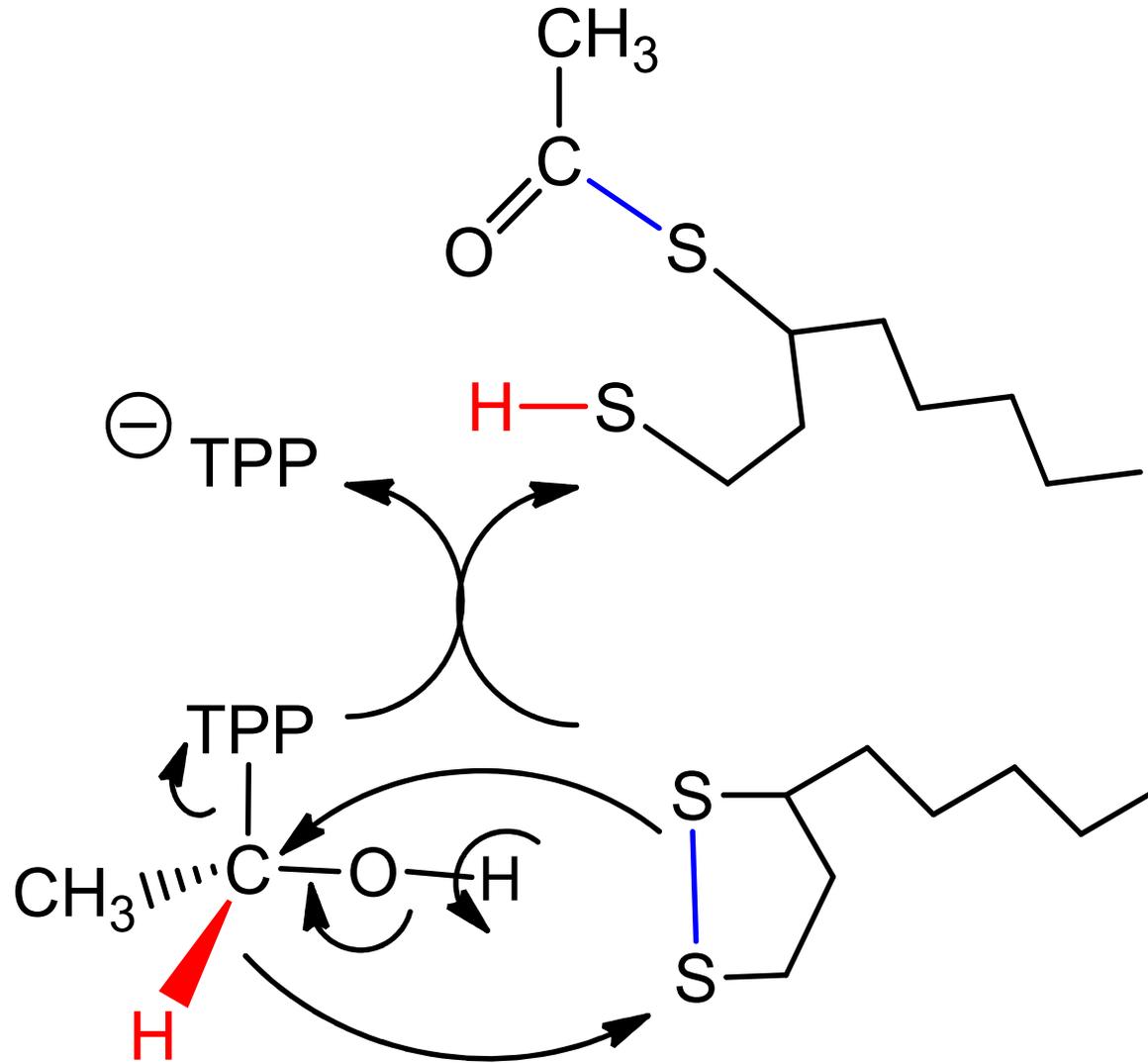
$$K_{\text{eq}} = 7.1 \times 10^5$$

Complesso della piruvato deidrogenasi: esempio di incanalamento dei substrati (*substrate channeling*)

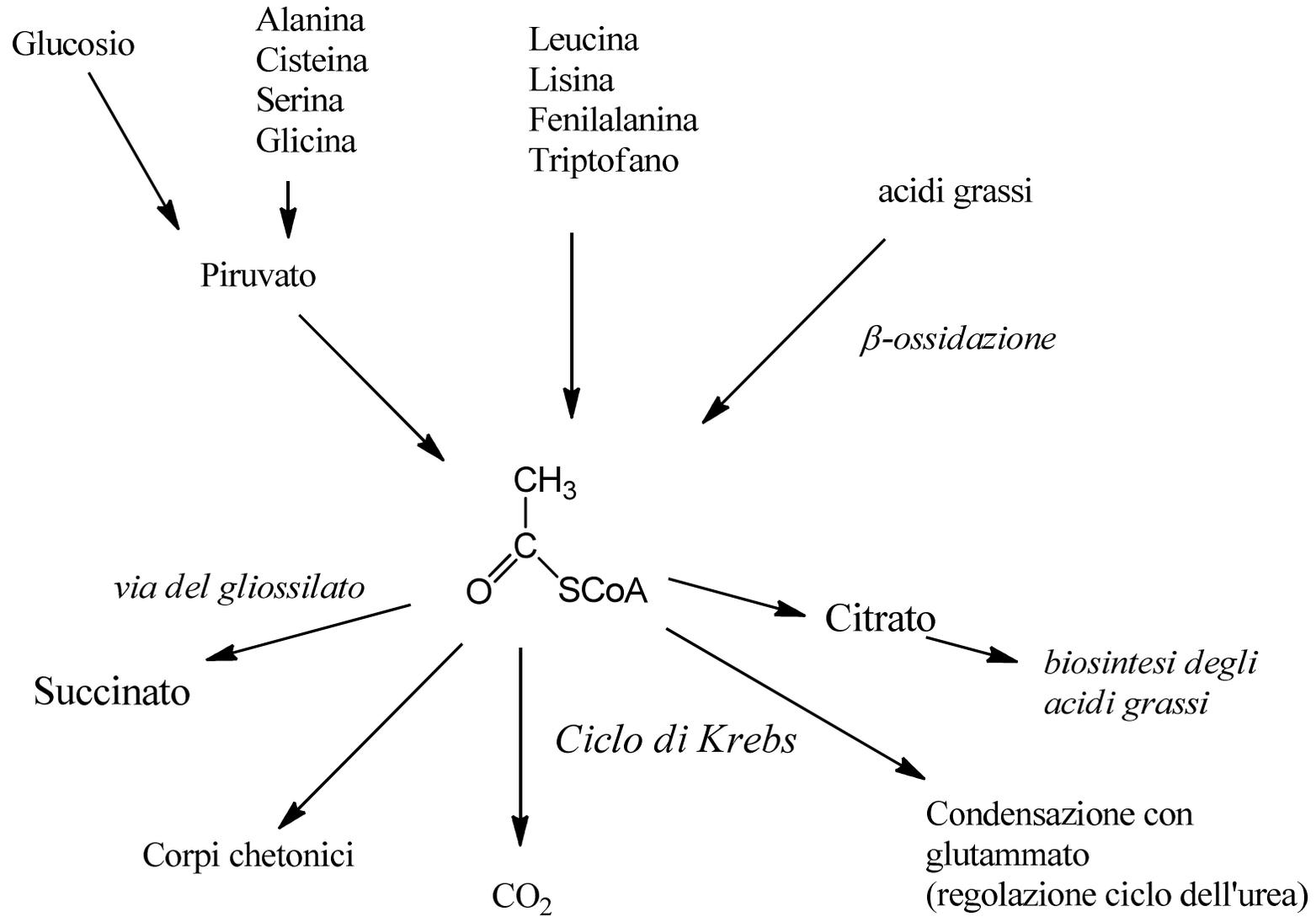




Ossidazione dell'idrossietilamina da parte della lipoil-lisina



Acetil-CoA: crocevia metabolico



Il ciclo di Krebs

(anche ciclo dell'acido citrico
o ciclo degli acidi tricarbossilici)

- 8 reazioni
- l'ultima rigenera il substrato della prima
- l'acetile è ossidato a CO_2
- vengono ridotti molti trasportatori di e^-
- gli intermedi sono precursori di vie biosintetiche: il ciclo di Krebs è di fatto una via **anfibolica**



Hans Krebs, 1900–1981
Nobel per la
Medicina nel 1953

Reazione 1. Citrato sintasi

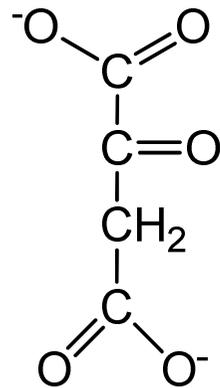


Reazione irreversibile ($\Delta G^{0'} = -32 \text{ kJ/mol}$)

L'ossalacetato deriva dall'ultima reazione del ciclo

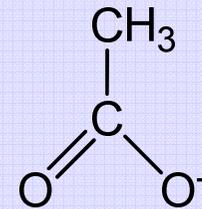
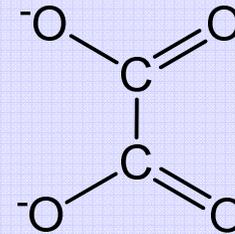
Reazione 1. Citrato sintasi

Meccanismo ordinato: l'ossalacetato è il primo ad entrare nel sito catalitico dell'enzima



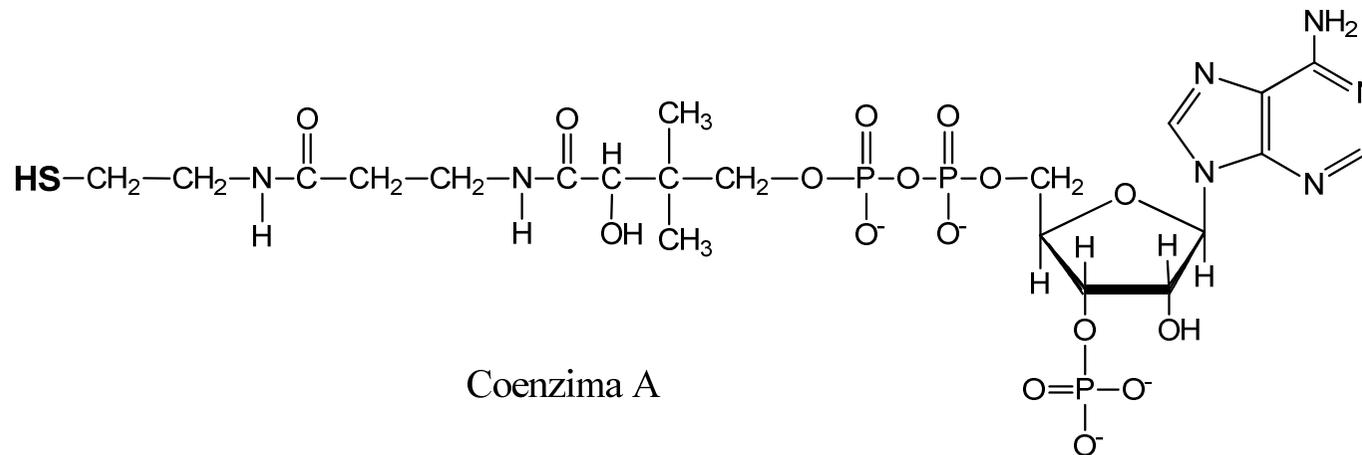
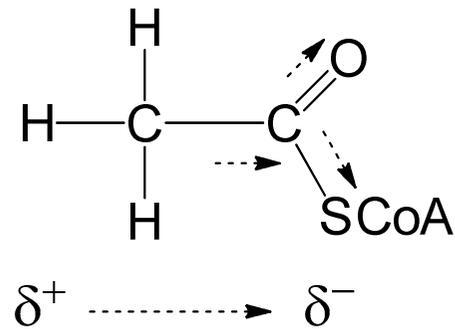
Ossalacetato

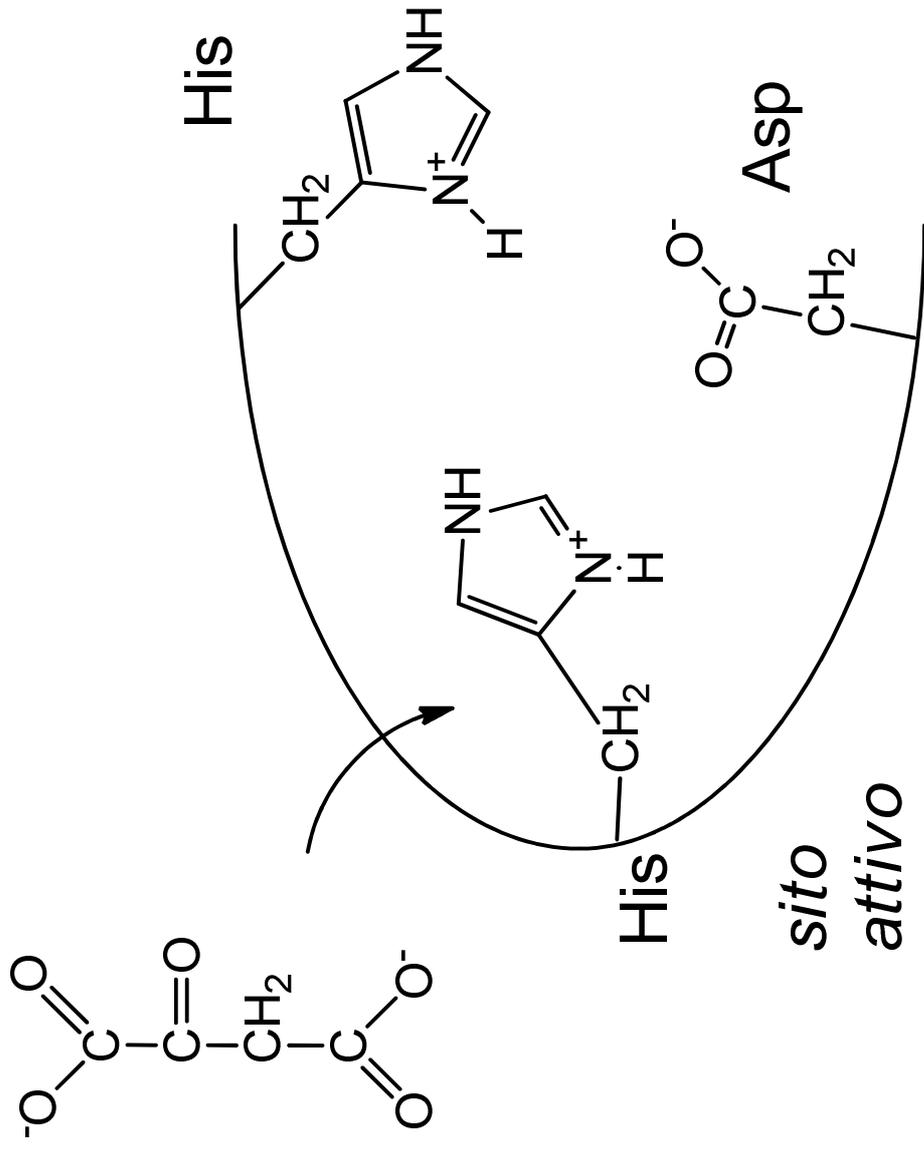
Ossalato



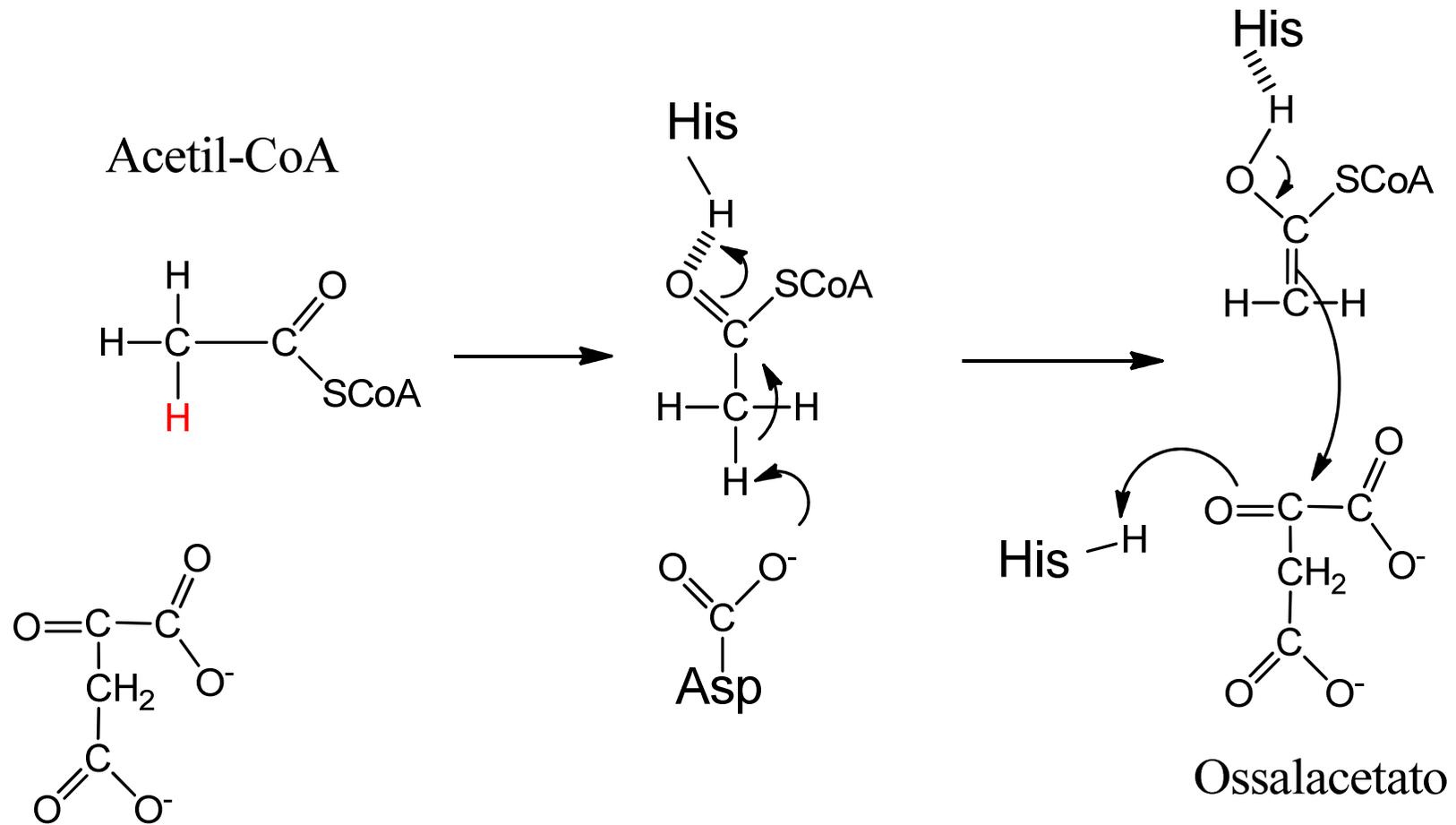
acetato

L'acetile dell'acetil-CoA è polarizzato
I protoni metilici sono lievemente acidi



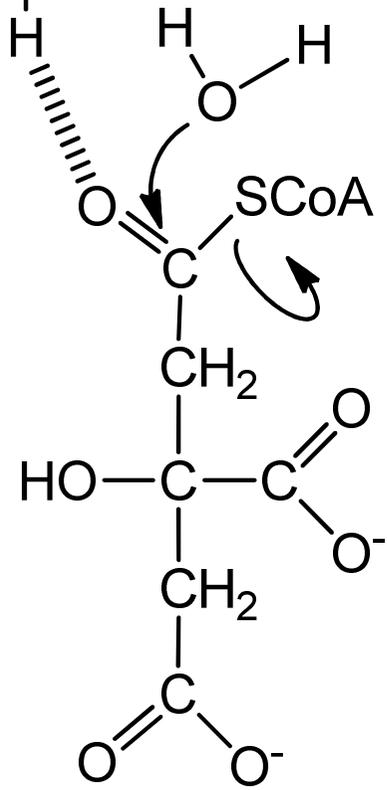


Citrato sintasi: condensazione

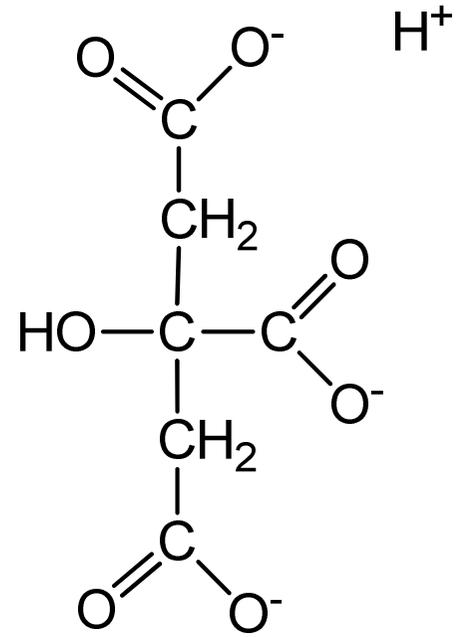
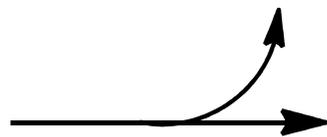


Citrato sintasi: idrolisi del citril-CoA

His

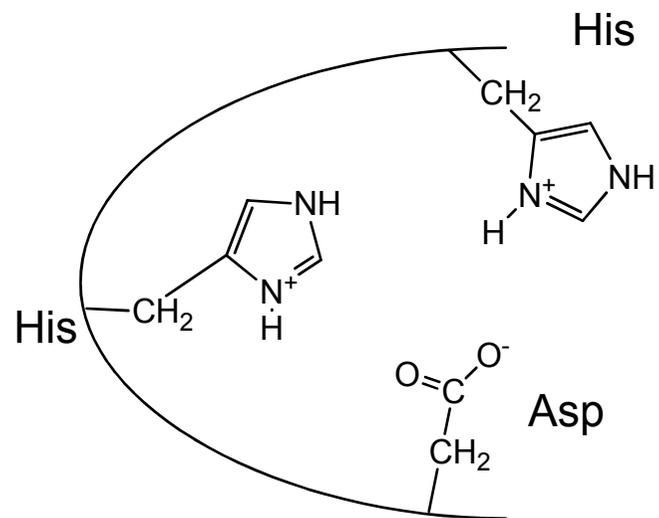
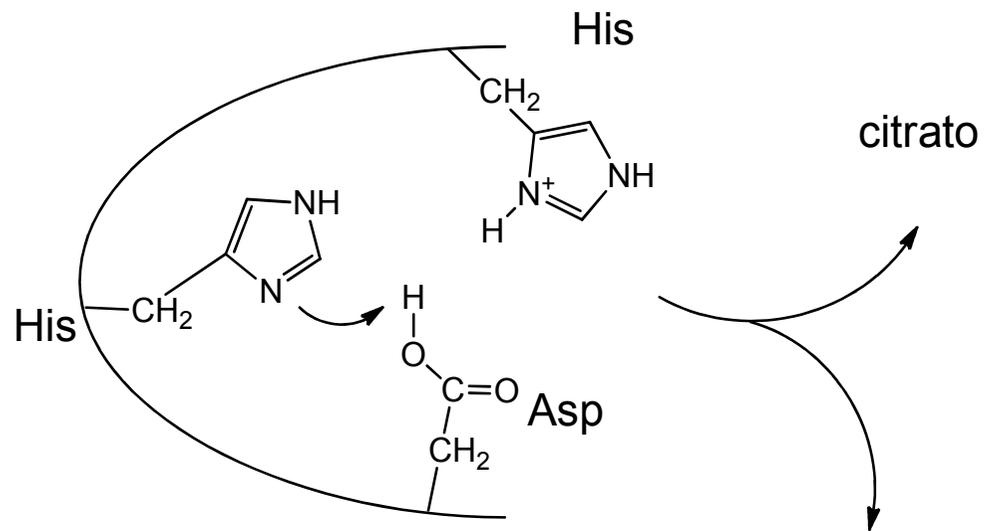


CoASH

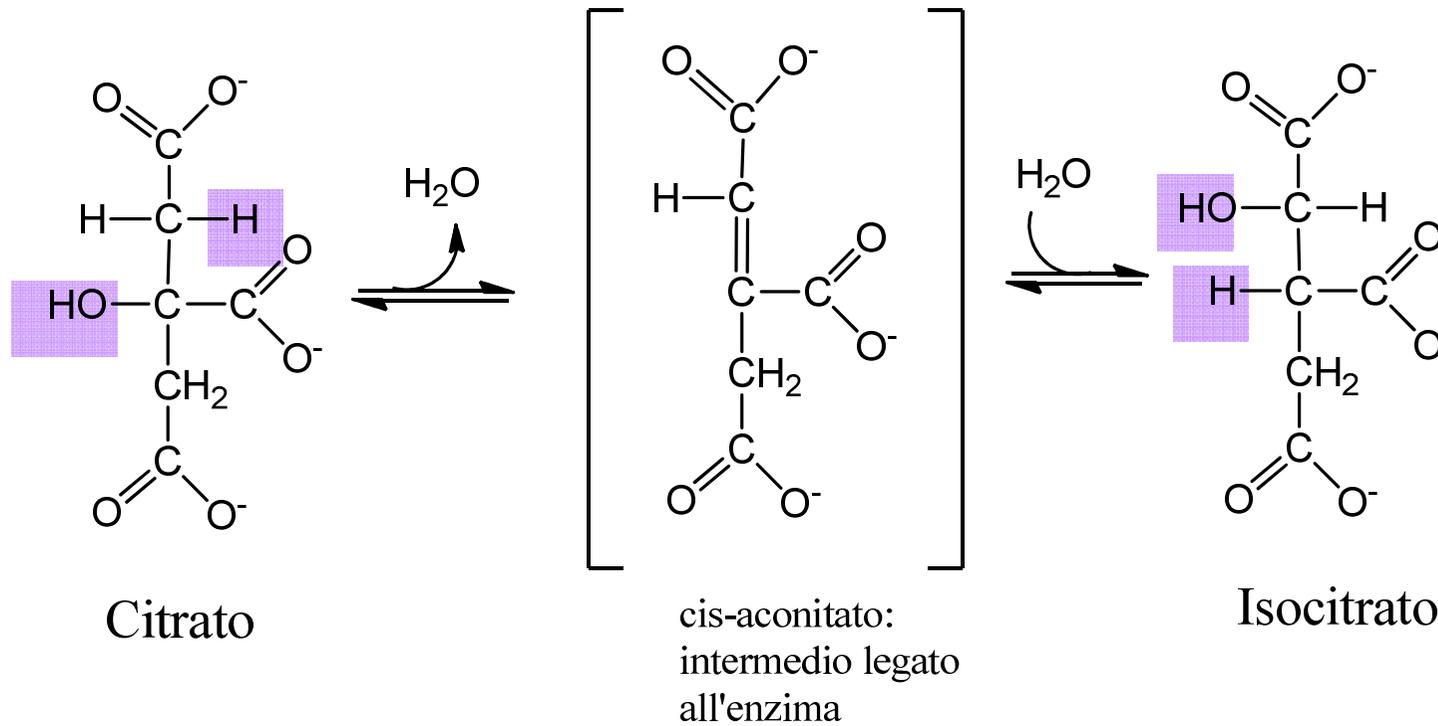


Citrato

Citryl-CoA
intermedio legato
all'enzima



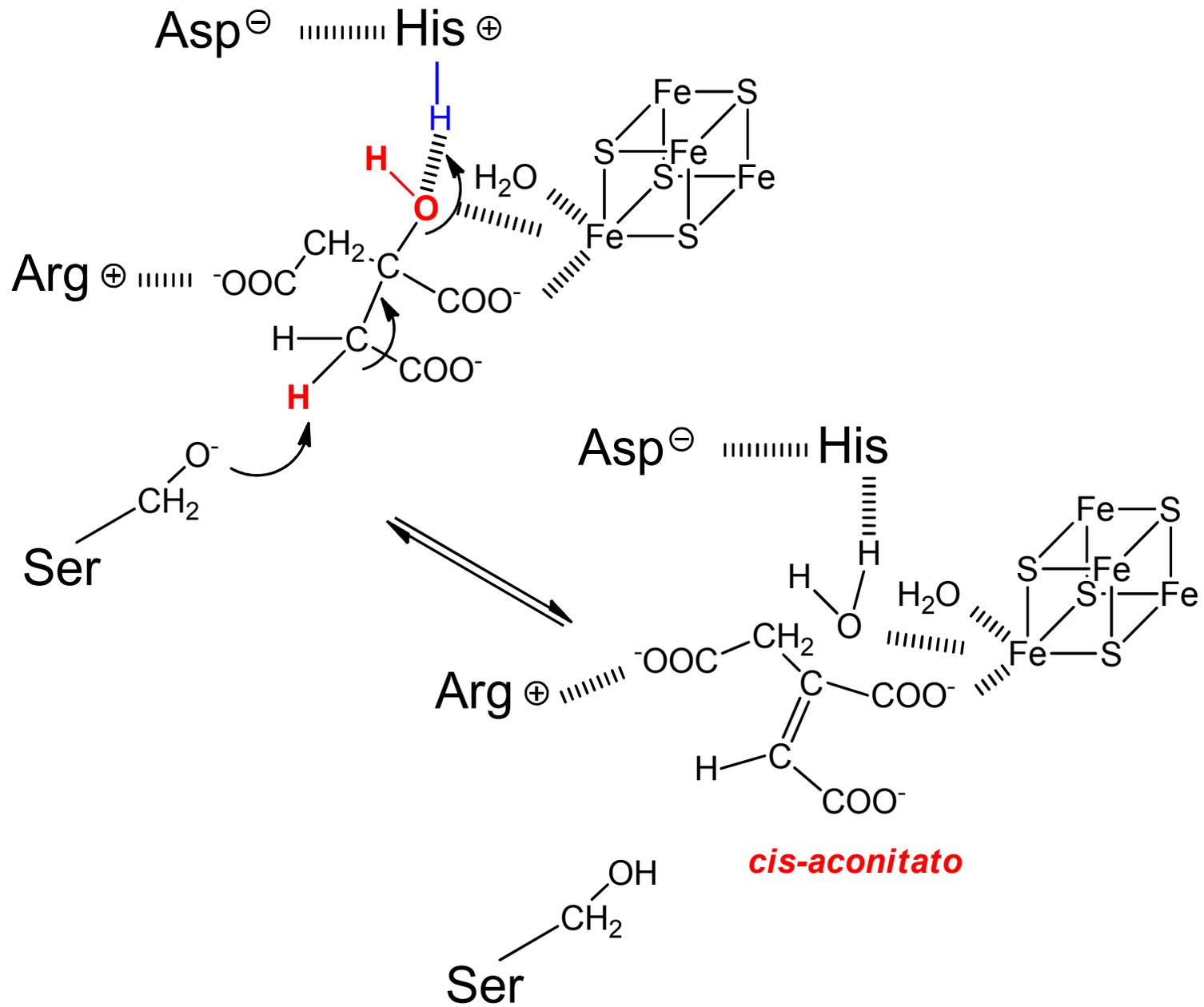
Reazione 2: isomerizzazione

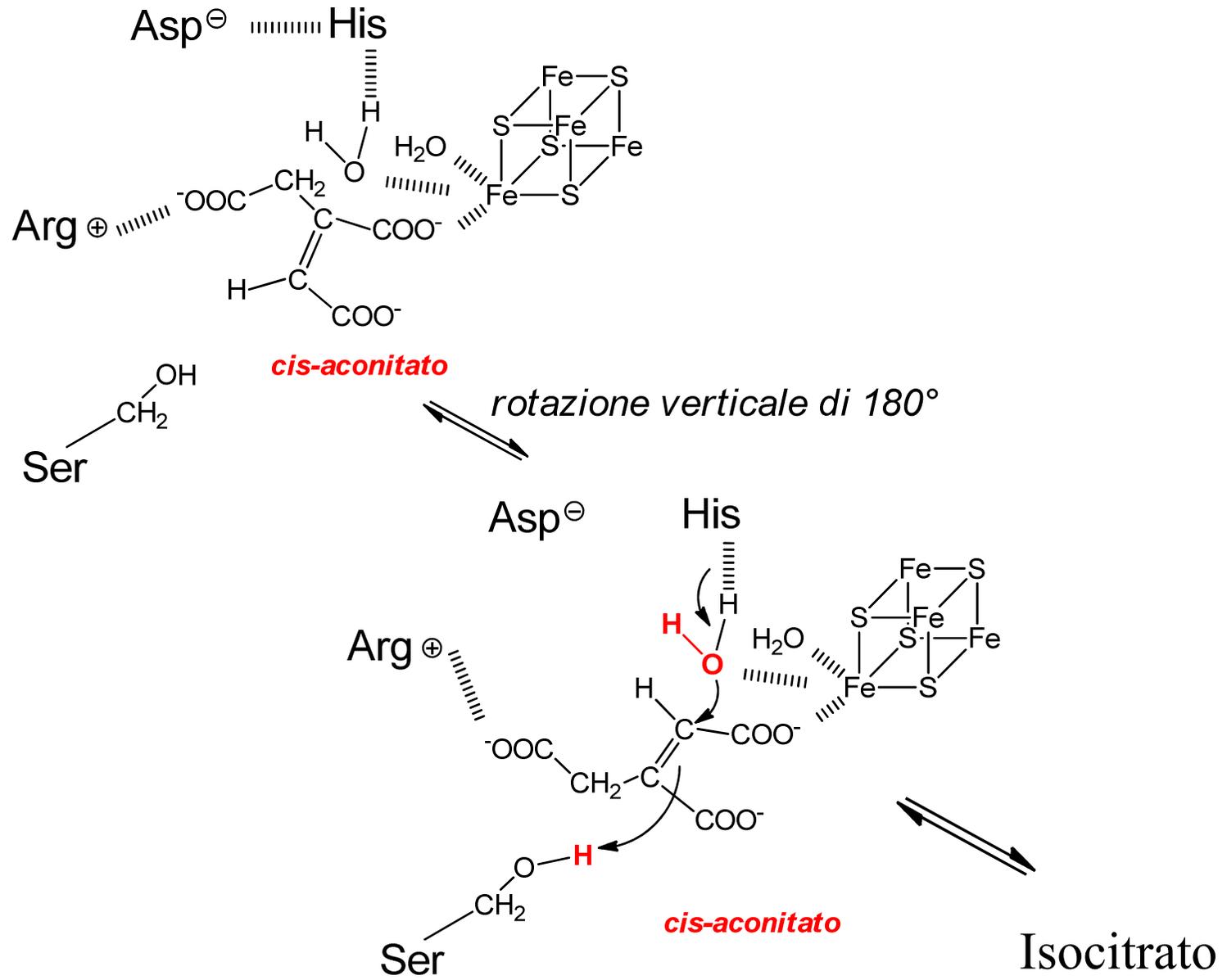


Aconitasi

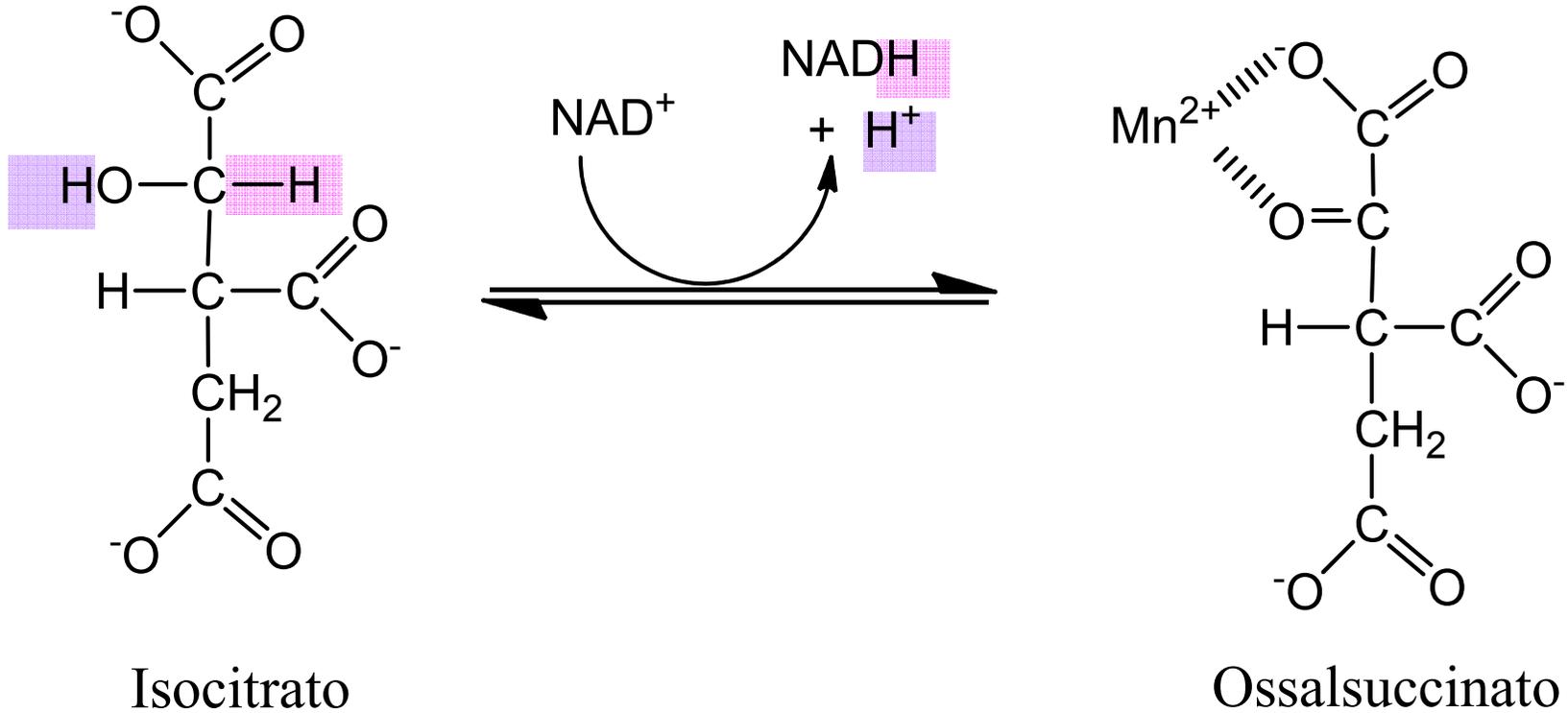
$$\Delta G^{\circ} = 13.3 \text{ KJ/mol}$$

$$K_{\text{eq}} = 4.7 \times 10^{-3}$$



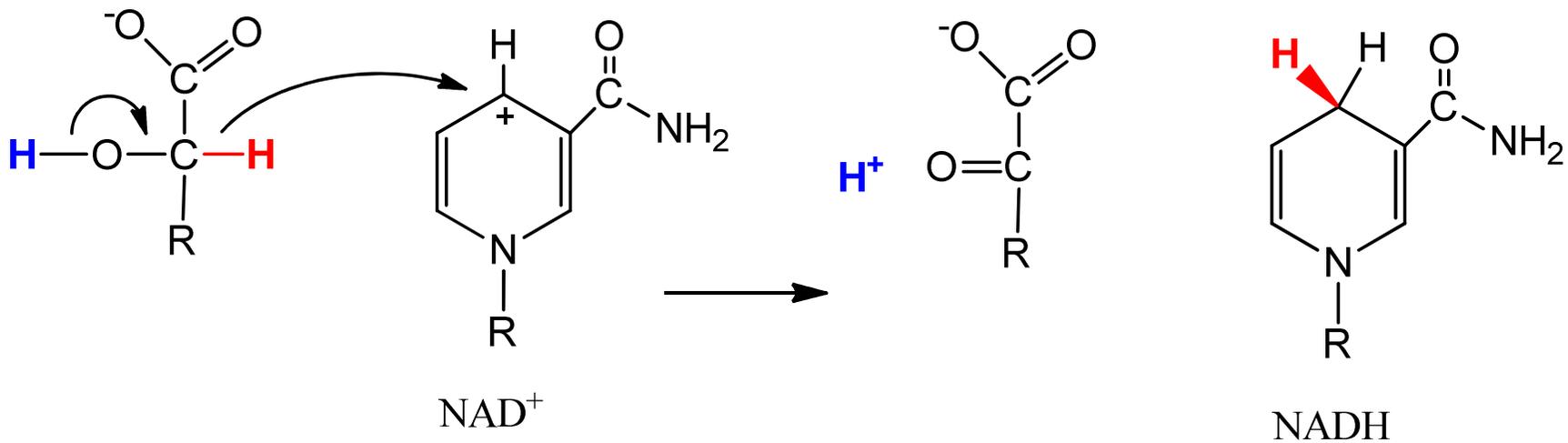


Reazione 3: 1a fase deidrogenazione

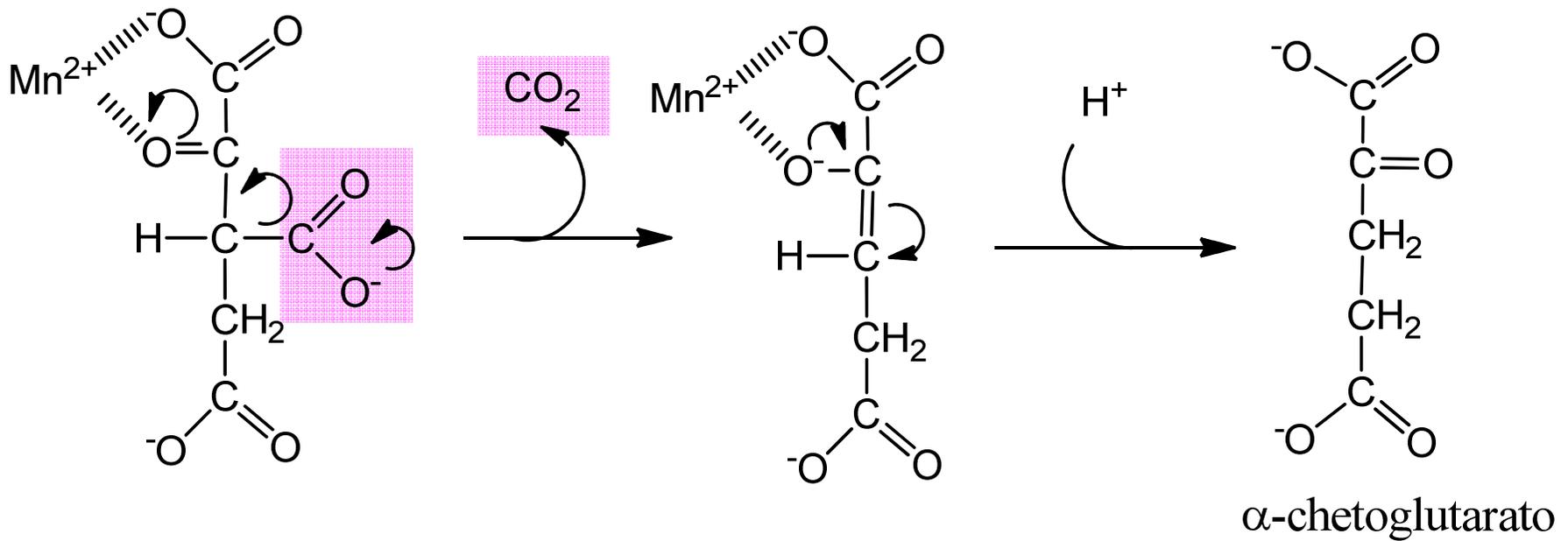


Isocitrato deidrogenasi. $\Delta G^{\circ'} = -21 \text{ kJ/mol}$

Deidrogenasi NAD dipendenti

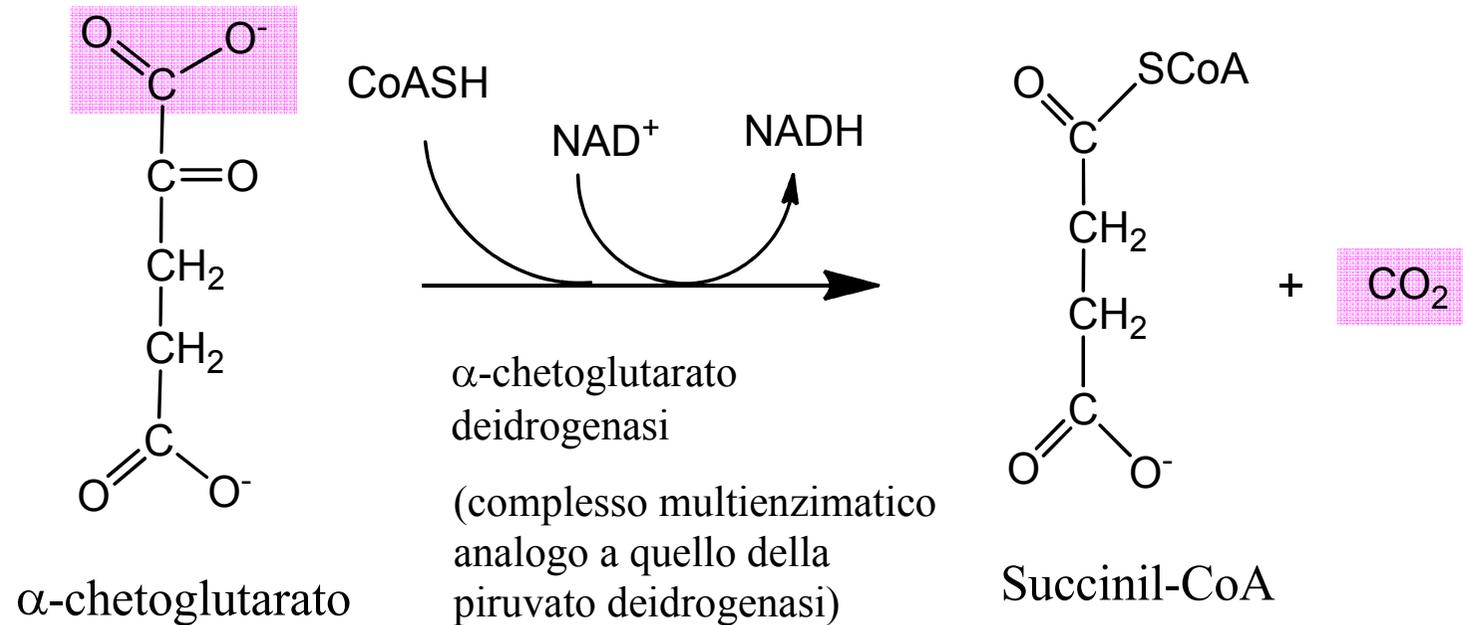


Reazione 3: seconda fase decarbossilazione



ossalsuccinato
(legato all'enzima)

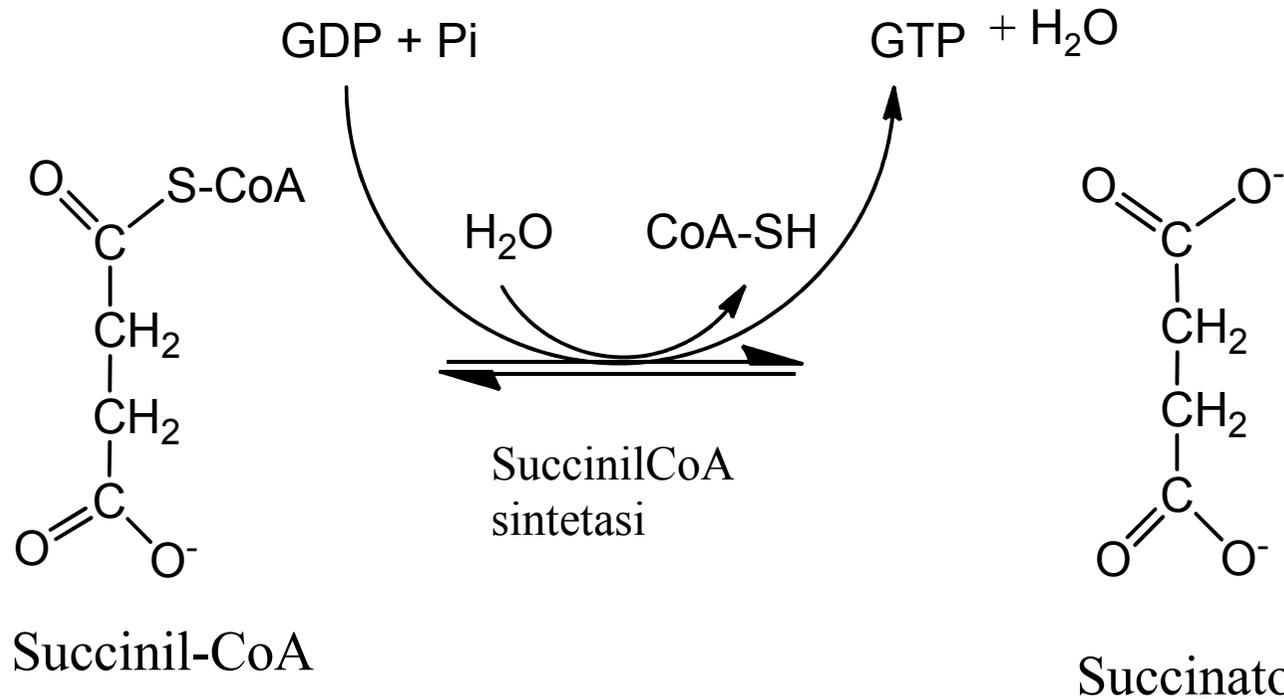
Reazione 4: si perde una seconda molecola di CO₂



$$\Delta G^{\circ'} = -33.5 \text{ KJ/mol}$$

$$K_{\text{eq}} = 7.4 \times 10^5$$

Reazione 5: l'energia del legame tioestere è conservata nella sintesi del GTP



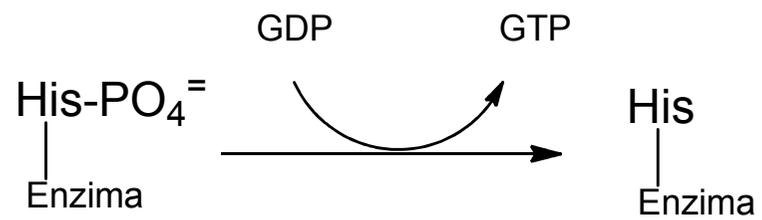
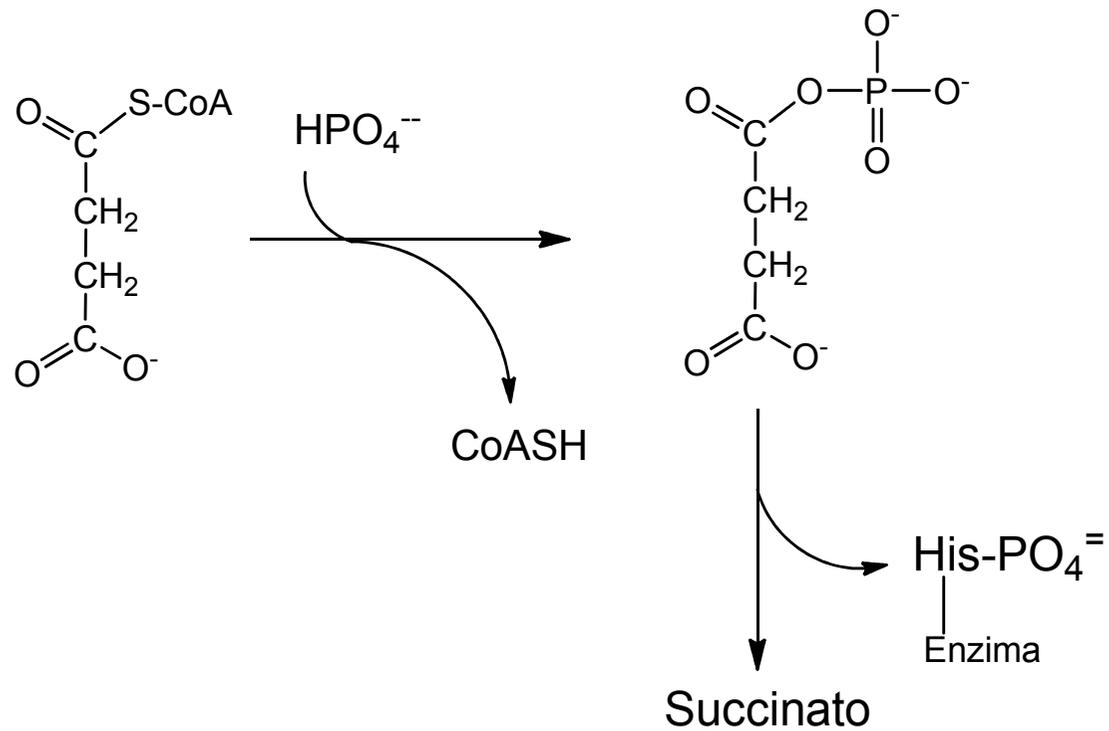
$$\Delta G^{\circ} = -2.9 \text{ kJ/mol}$$

$$K_{\text{eq}} = 3.2$$

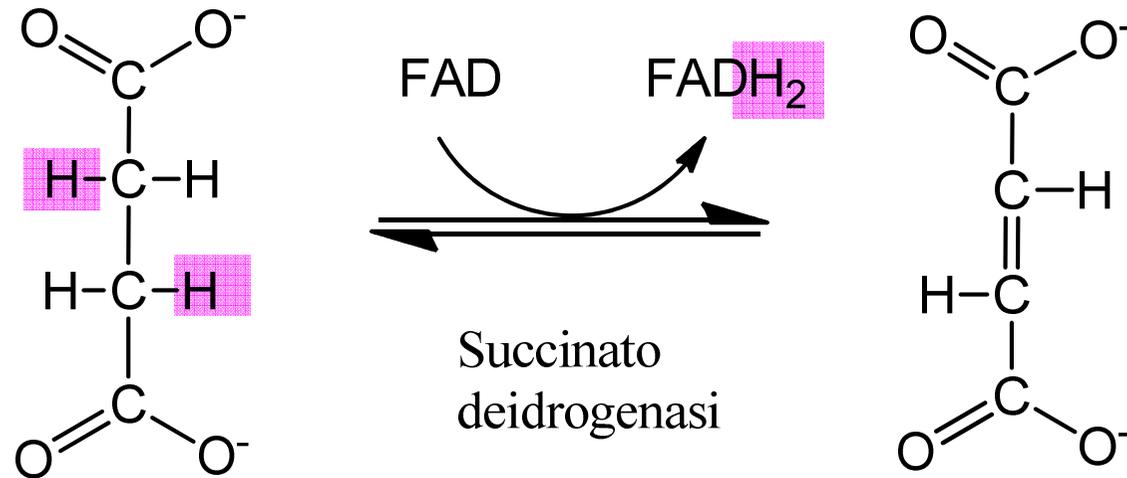
Lavoisier 1790 da *succinum*
(=ambra) da cui veniva distillato



Succinil-CoA sintetasi



Reazione 6: ossidazione con FAD



Succinato

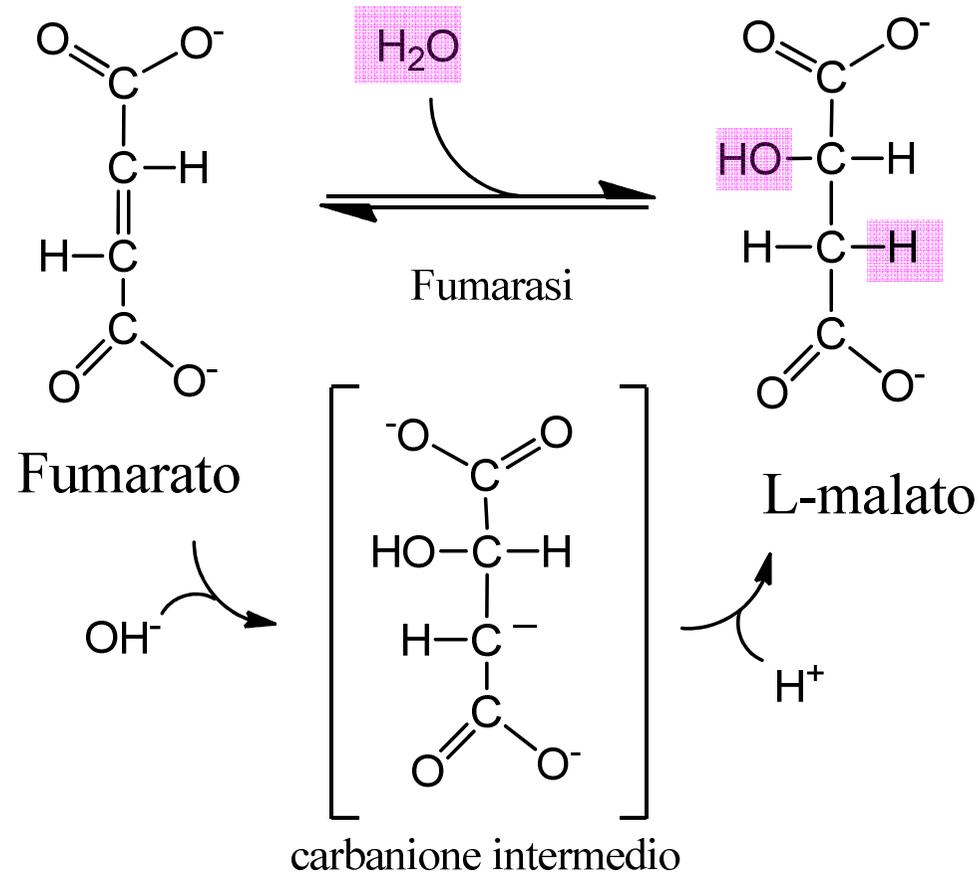
Fumarato

Lassaigne 1819 da
Fumaria officinalis

$$\Delta G^{\circ'} = 0 \text{ KJ/mol}$$

$$K_{\text{eq}} = 1$$

Reazione 7: idratazione stereospecifica

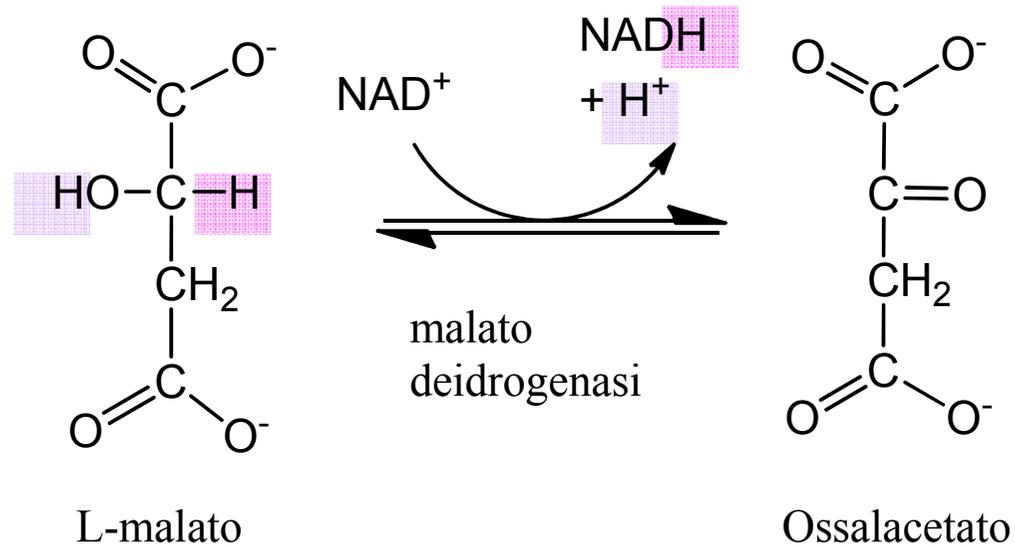


Acido malico, Scheele, 1786
da *malum* mela

$$\Delta G^{\circ'} = -3.8 \text{ KJ/mol}$$

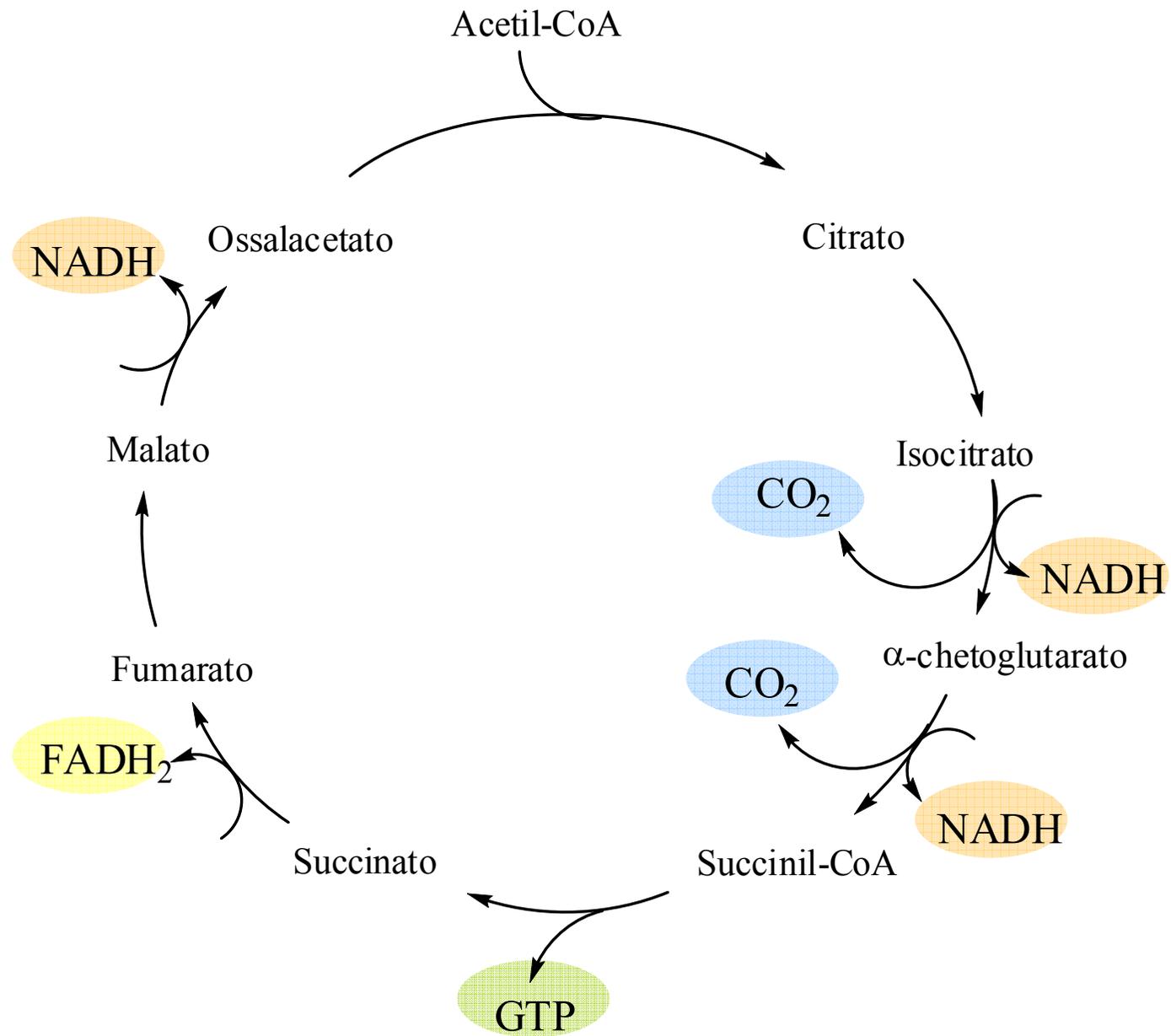
$$K_{\text{eq}} = 3.3$$

Reazione 8: si regenera l'ossalacetato substrato della prima reazione

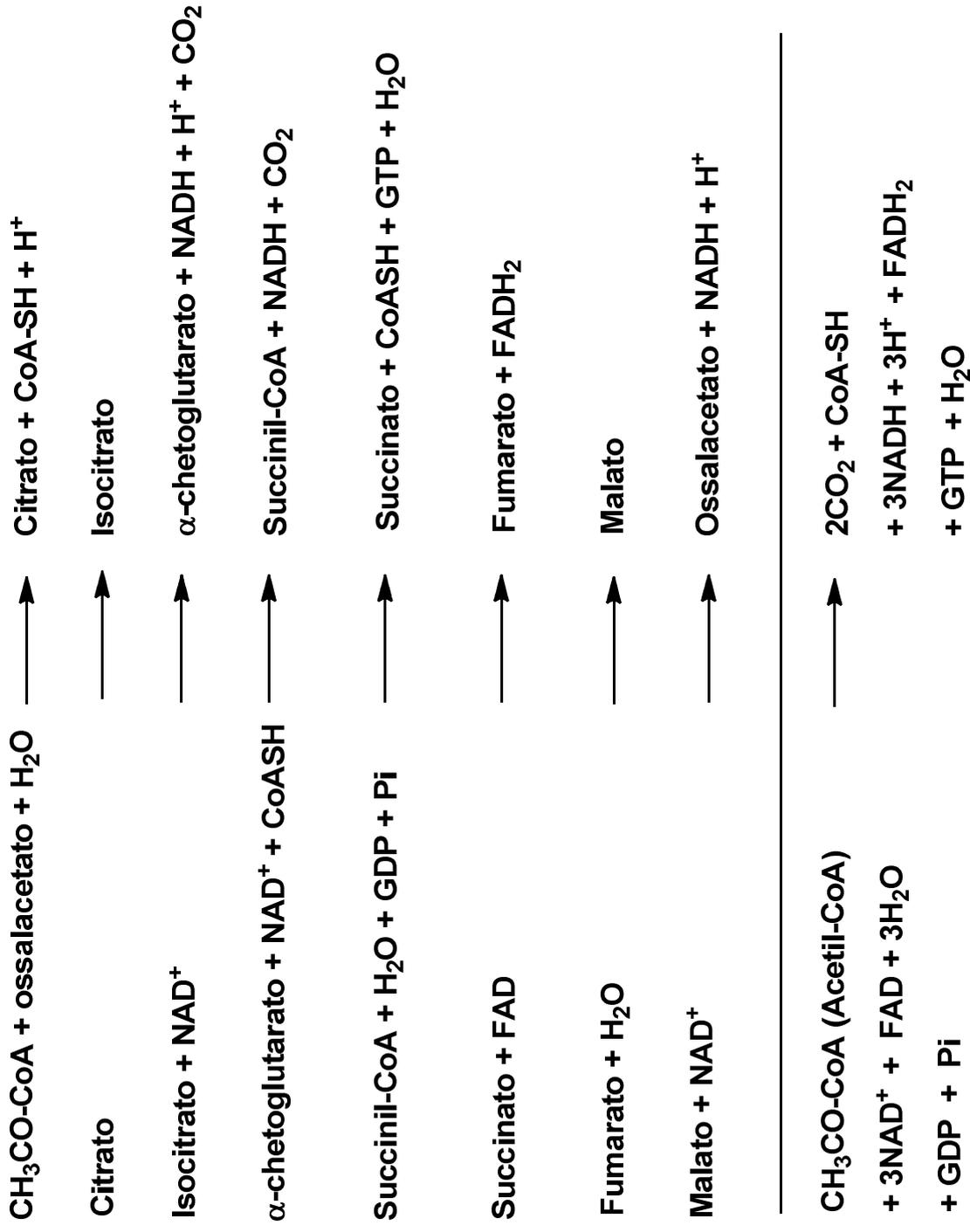


$$\Delta G^{\circ} = 29 \text{ kJ/mol}$$

Riepilogo

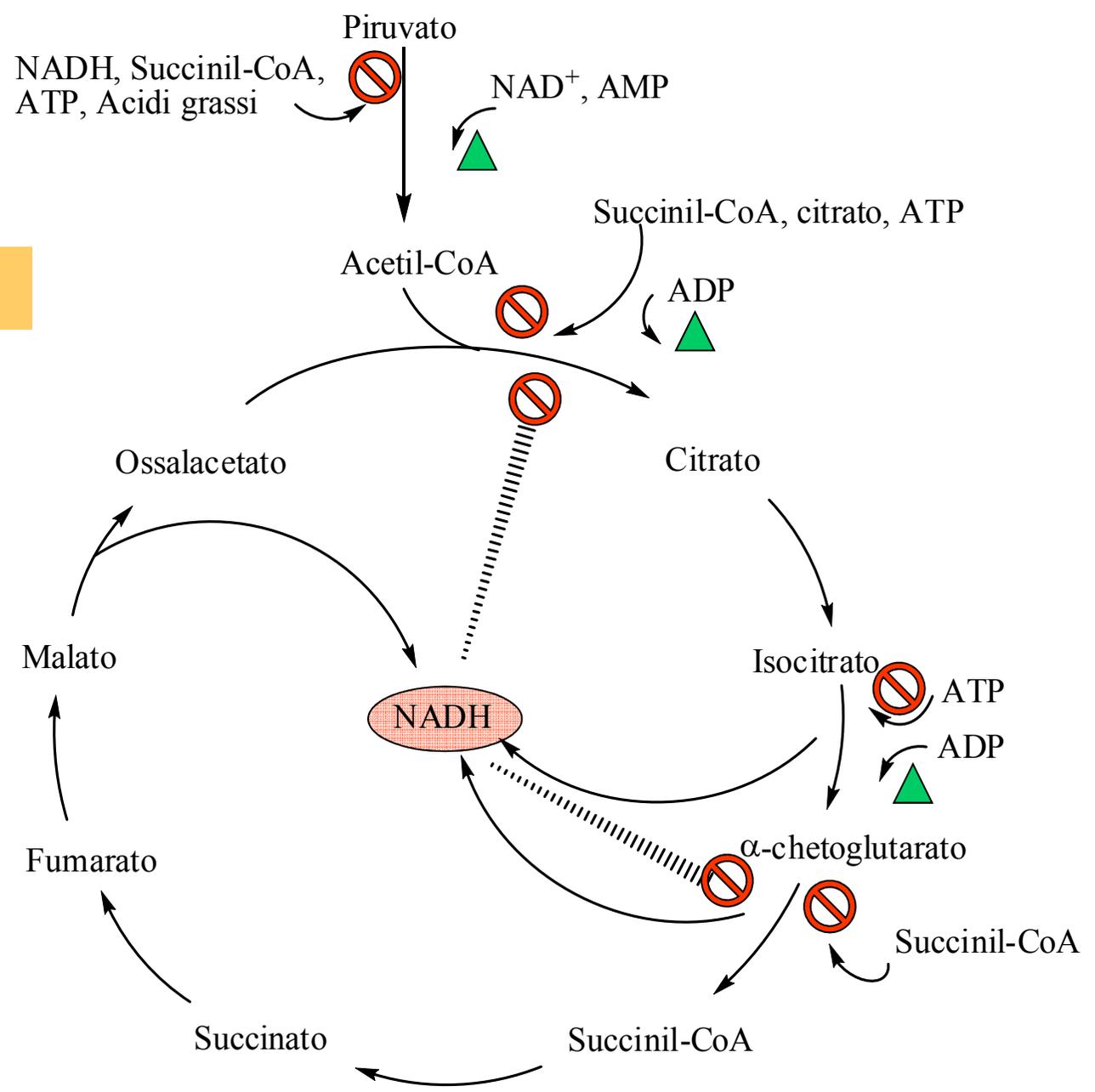


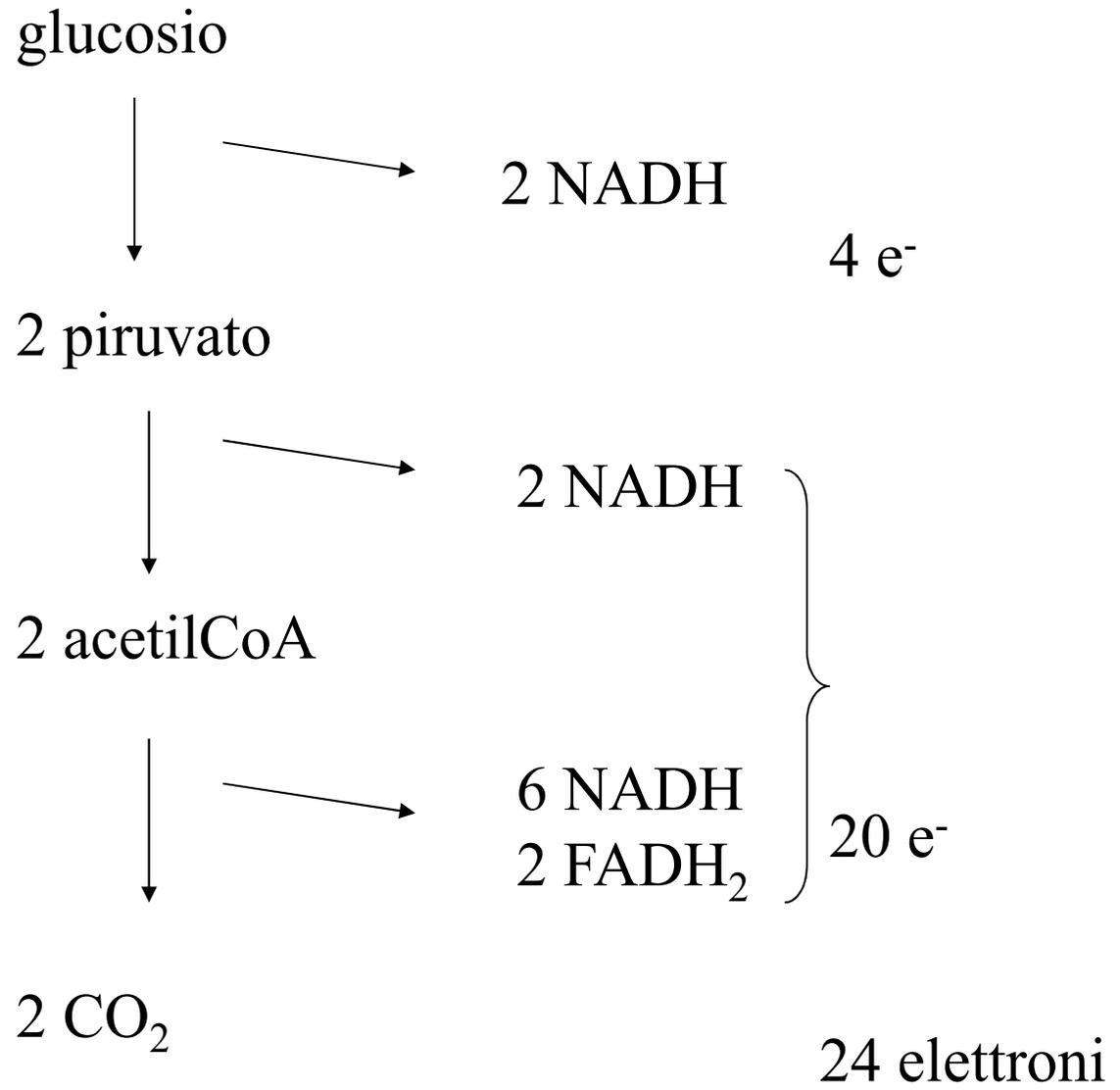
Ciclo di Krebs. Bilancio



Regolazione

▲ = attivazione
⊘ = inibizione



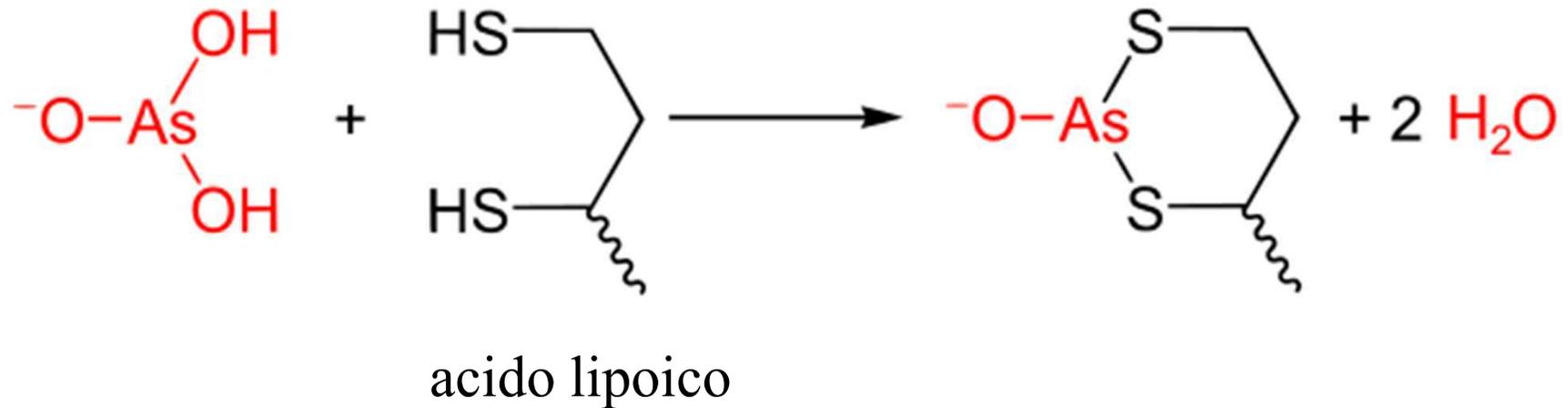


24 elettroni



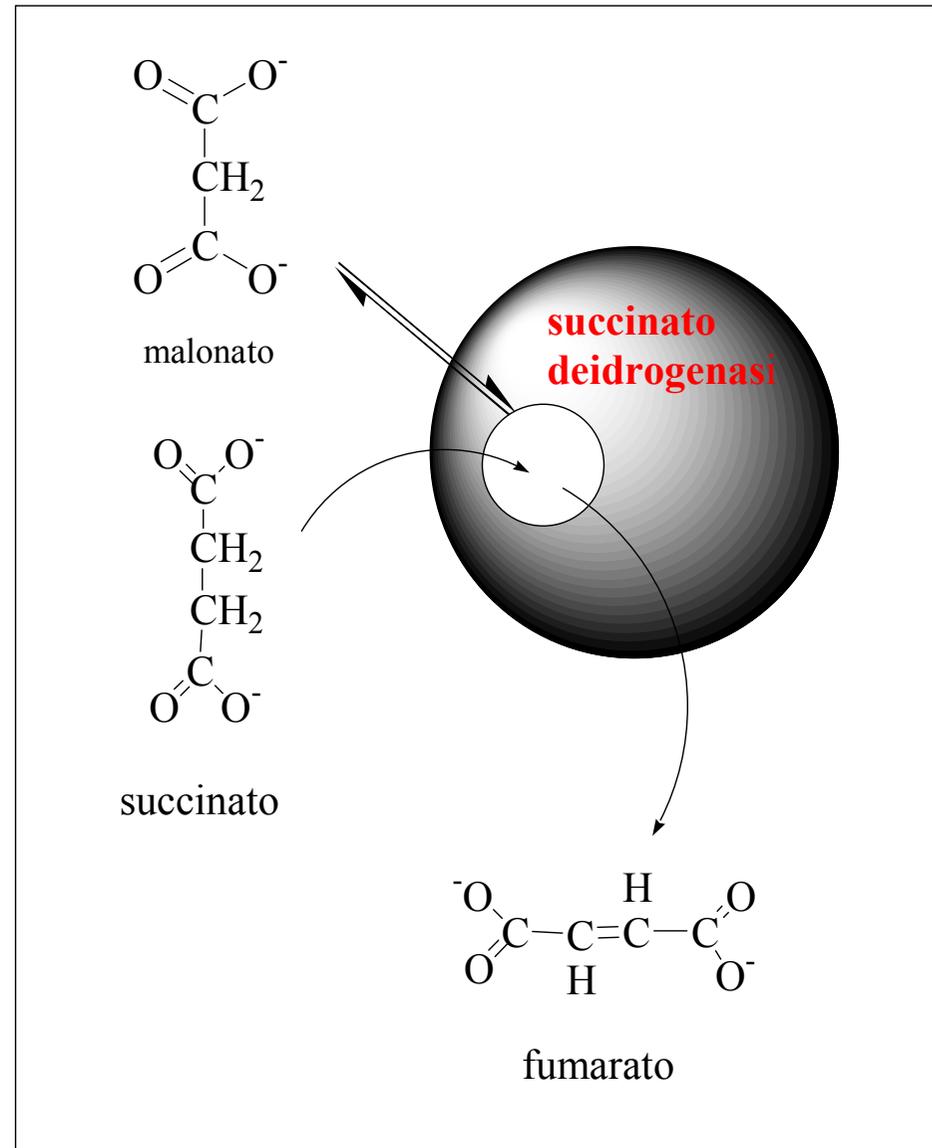
6 molecole di ossigeno

Tossicità dell'arsenito e degli arsenicali:
inibizione della piruvato deidrogenasi e
alfa-chetoglutarato deidrogenasi



Arsenicale medicamentoso

Inibizione da malonato: inibizione competitiva con succinato della succinato deidrogenasi

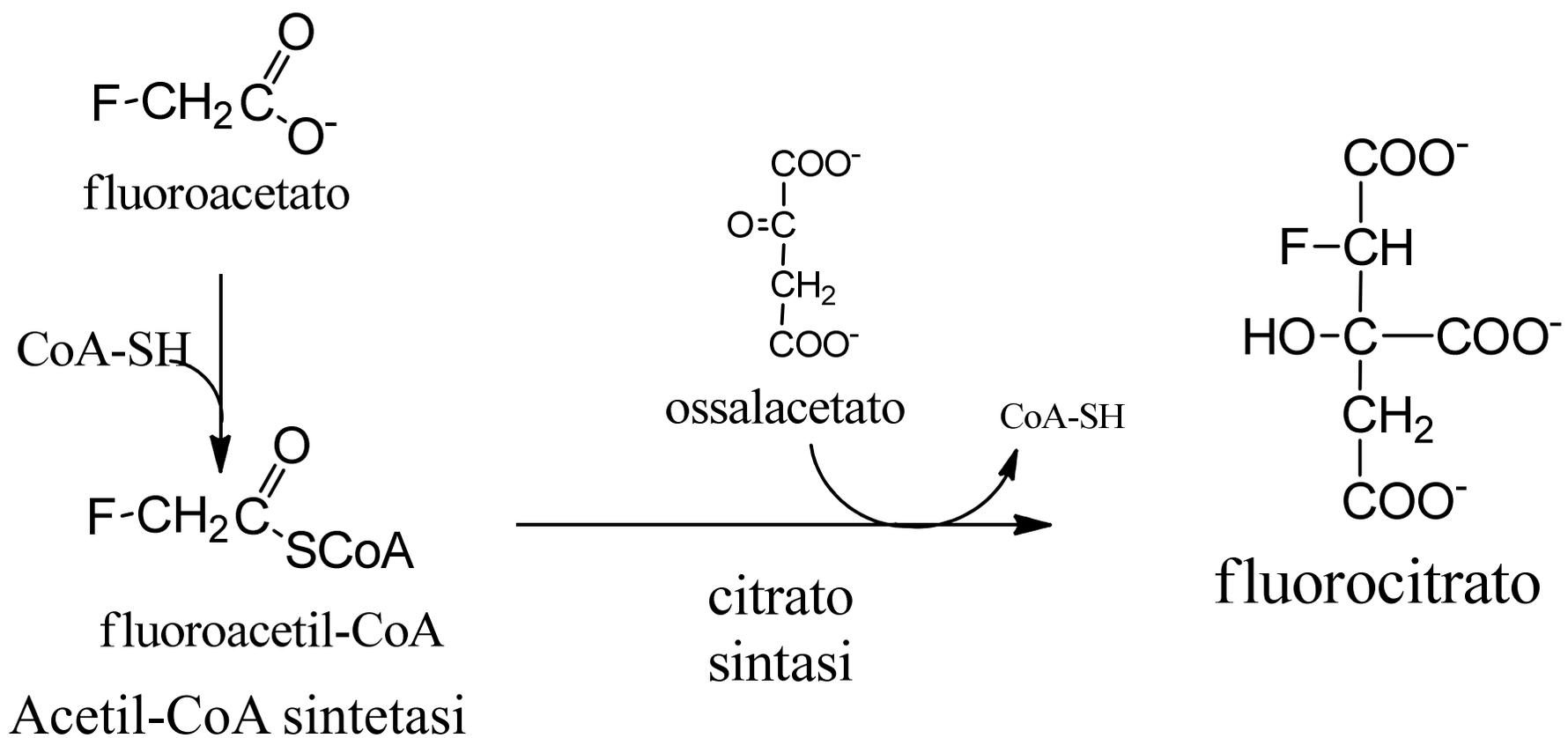


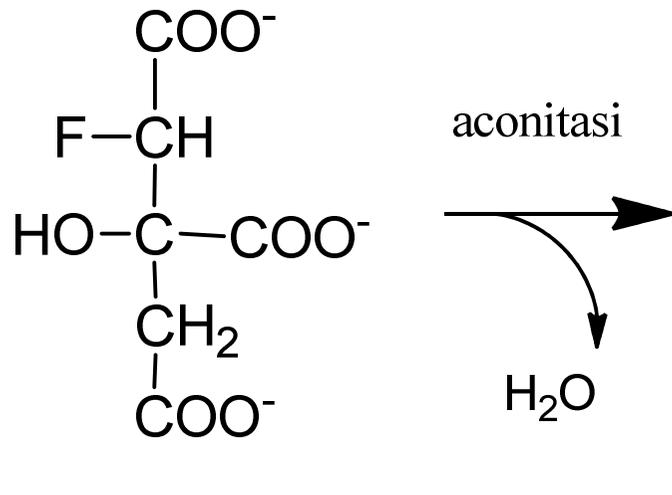
SODIO FLUOROACETATO (noto anche come 1080)

Potente inibitore del ciclo di Krebs:
inibisce la formazione di isocitrato

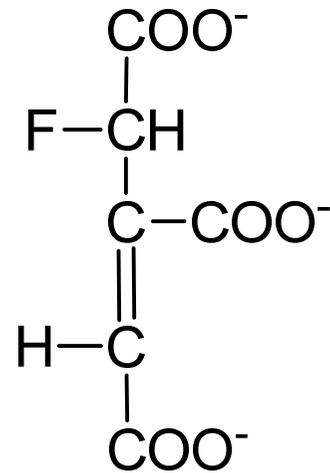
Accumulato in molte piante australiane,
tossiche per molti erbivori tranne che per i
canguri e affini

Rodenticida utilizzato in Australia e
Nuova Zelanda

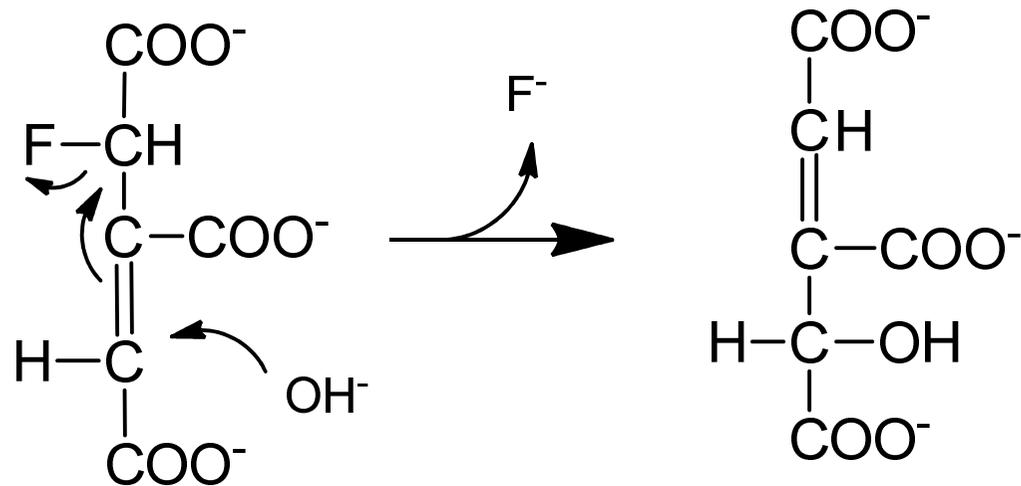




fluorocitrato

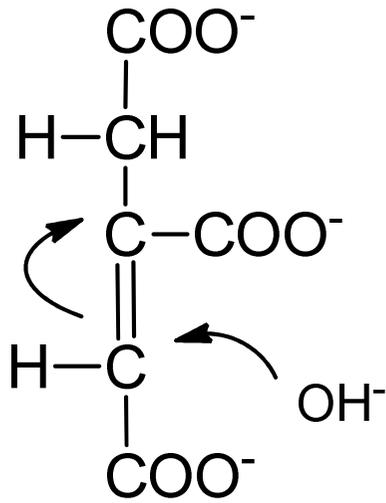


fluoro-*cis*-aconitato

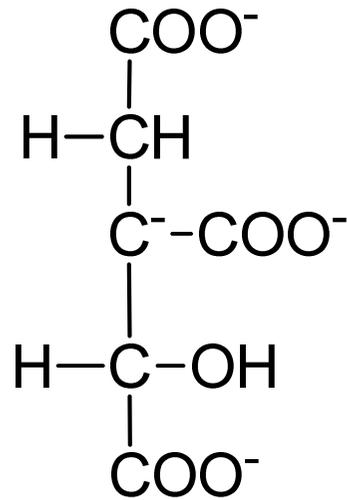


4-idrossi-*trans*-aconitato

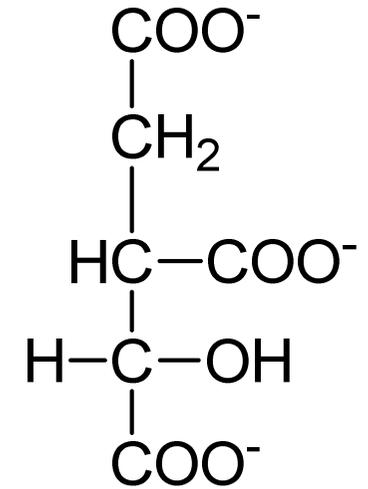
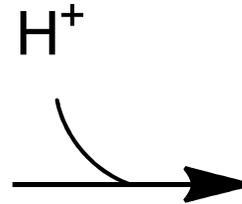
Inibitore ad alta affinità



cis aconitato
 aggiunta di acqua
 (prima l'idrossile
 poi il protone)

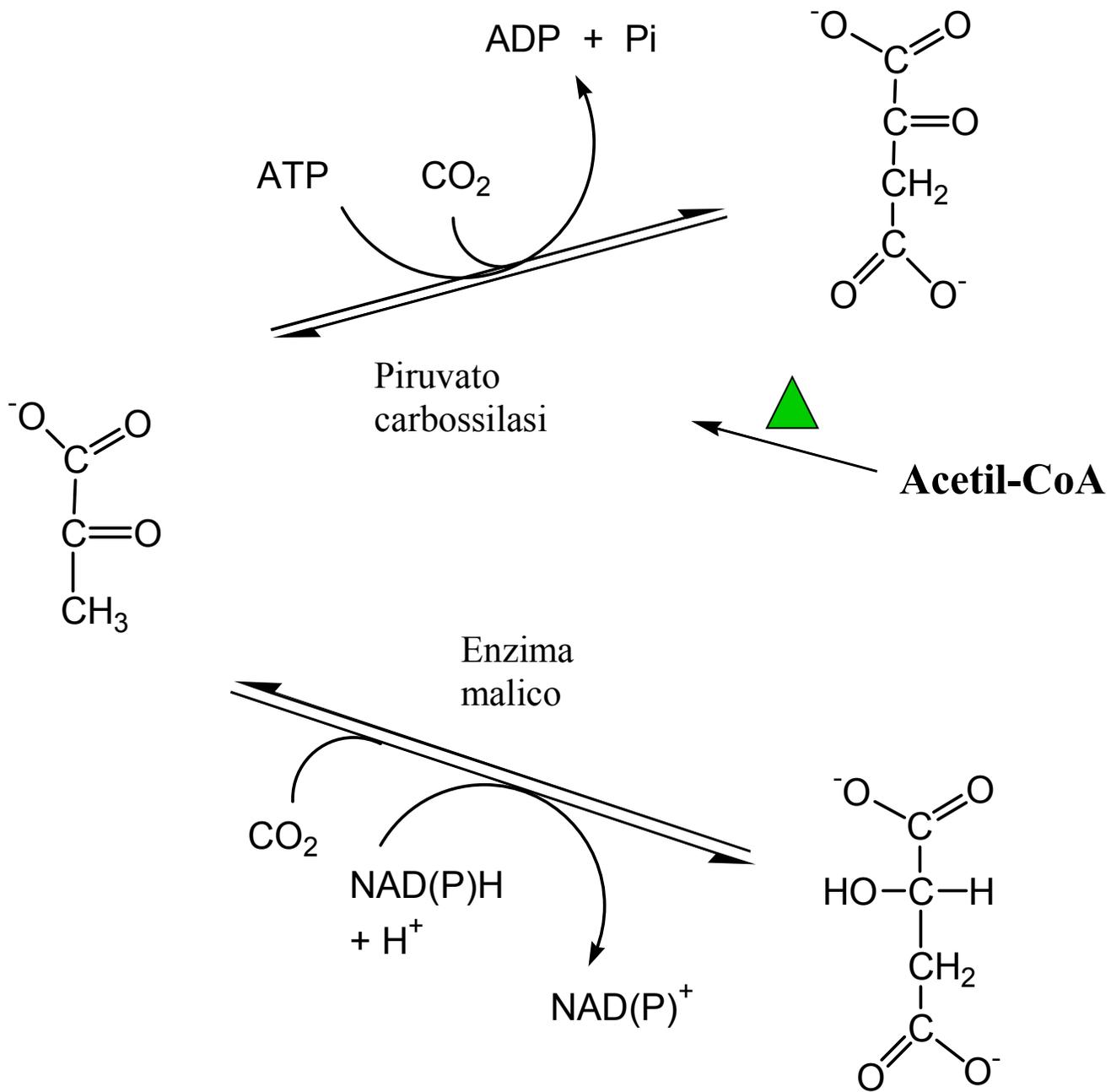


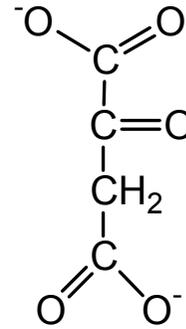
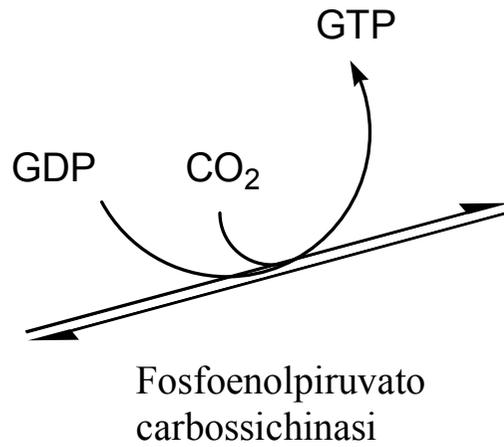
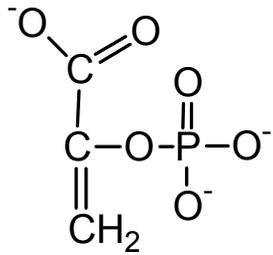
intermedio
 carbanionico



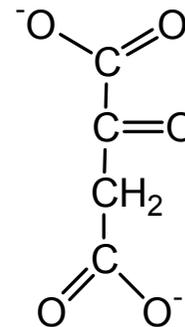
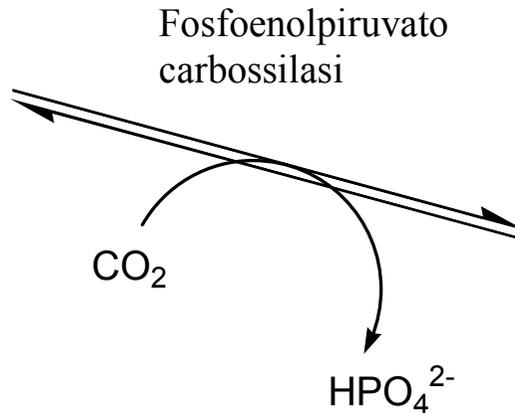
isocitrato

Reazioni anaplerotiche



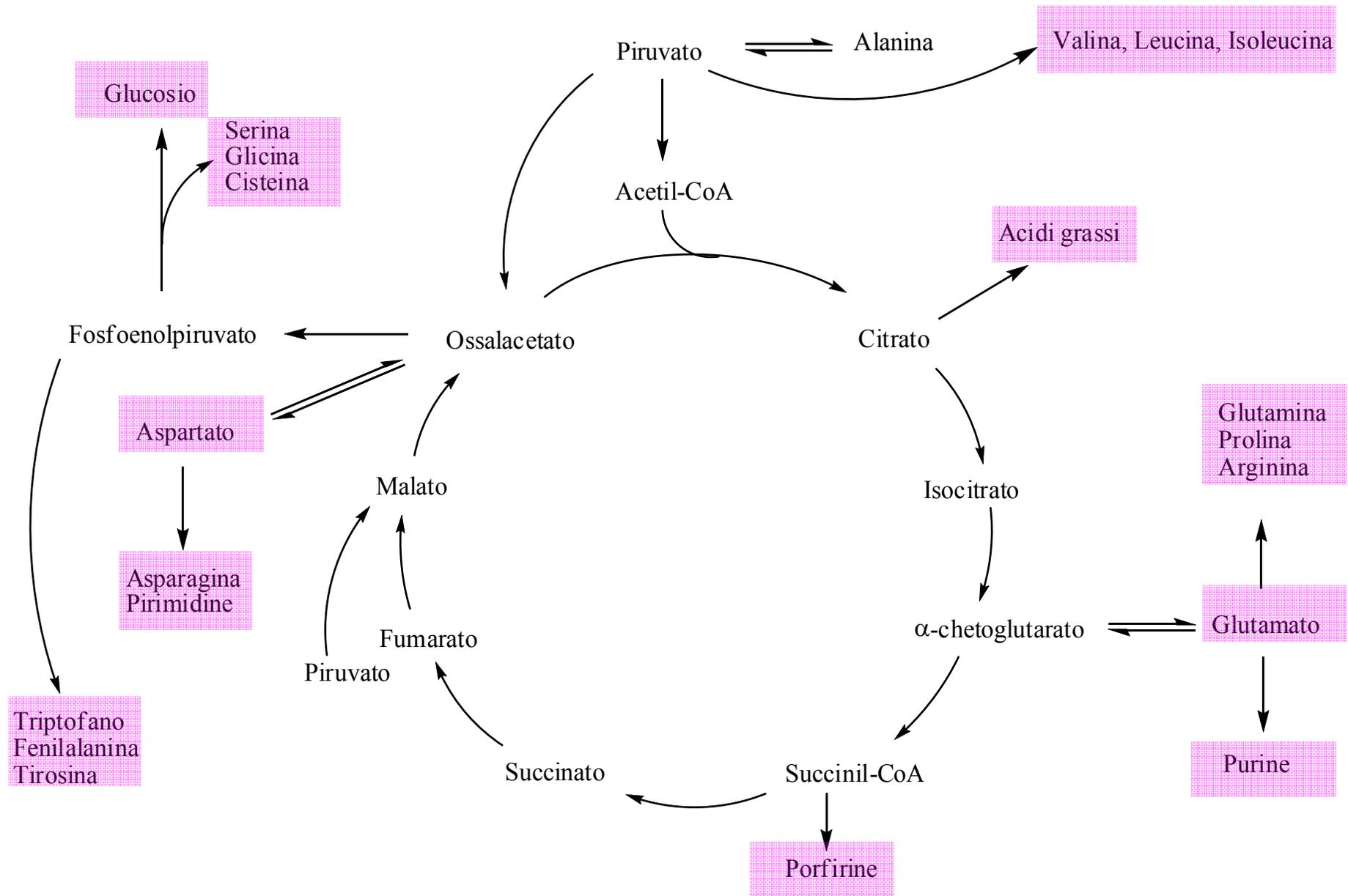


Cuore e muscolo
scheletrico,
attivato da fruttosio-1,6-
bisfosfato che si accumula se
il ciclo di Krebs lavora il
piruvato troppo lentamente

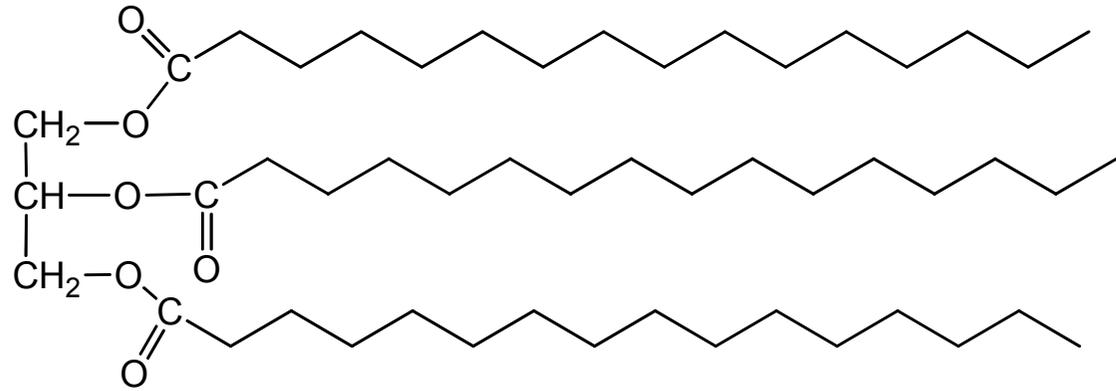


Cellule vegetali,
lieviti e batteri

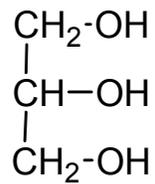
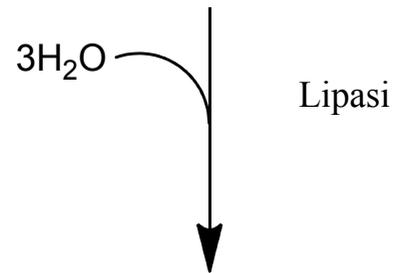
Ruolo del ciclo di Krebs nell'anabolismo



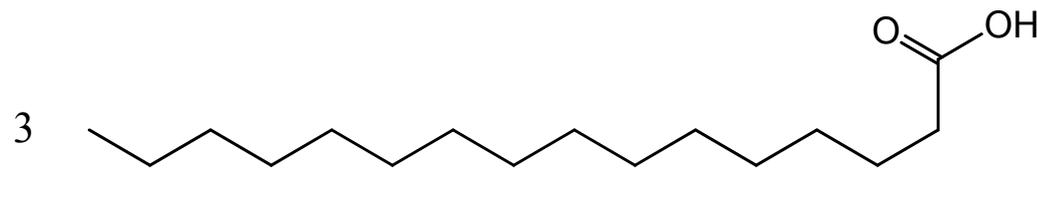
Ossidazione degli acidi grassi



triacilglicerolo

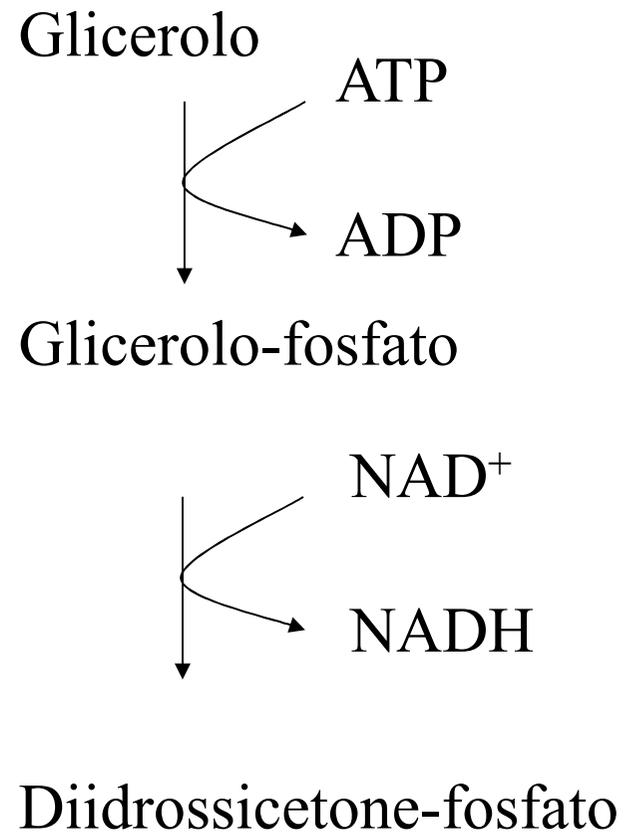


Glicerolo



Acido palmitico

Il glicerolo entra in glicolisi



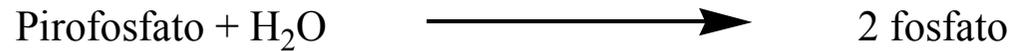
Attivazione degli acidi grassi



Acil-CoA sintetasi

$$\Delta G^{\circ'} = -15 \text{ KJ/mol}$$

$$K_{\text{eq}} = 425$$

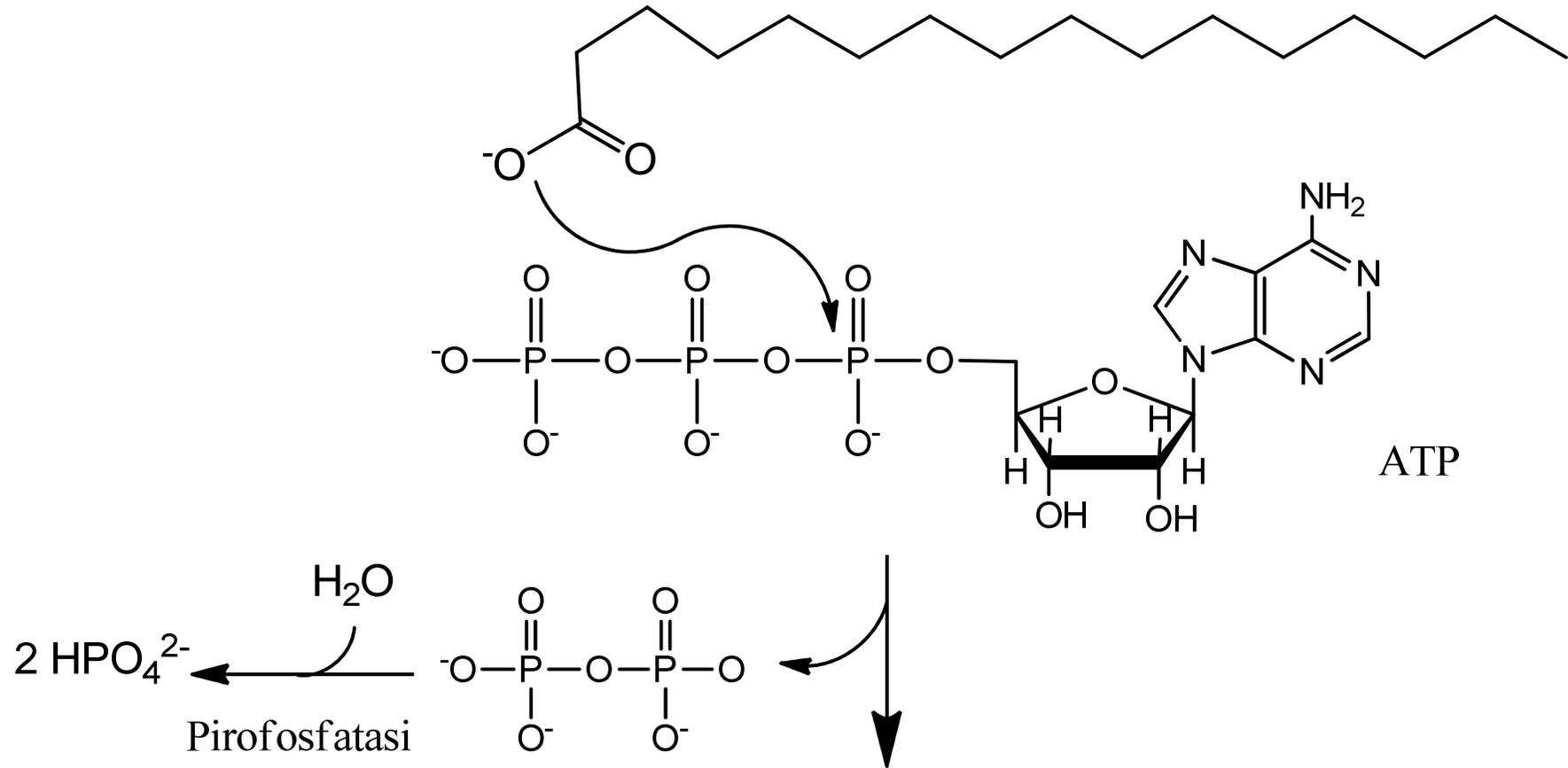


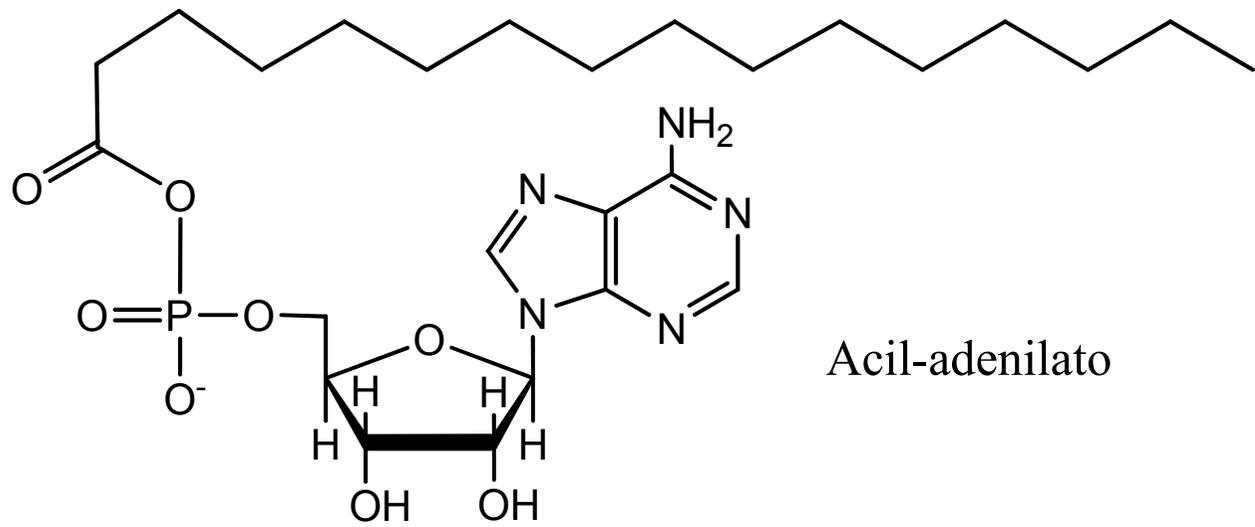
Pirofosfatasi

$$\Delta G^{\circ'} = -19 \text{ KJ/mol}$$

Enzima: AcilCoA sintetasi

Acido grasso



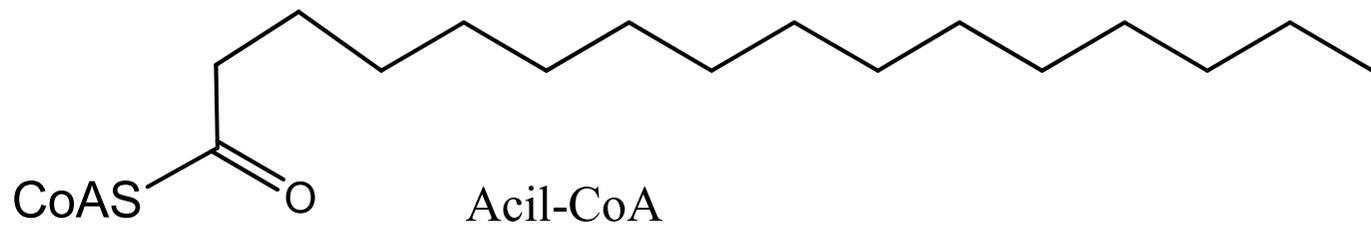


Acil-adenilato

CoASH

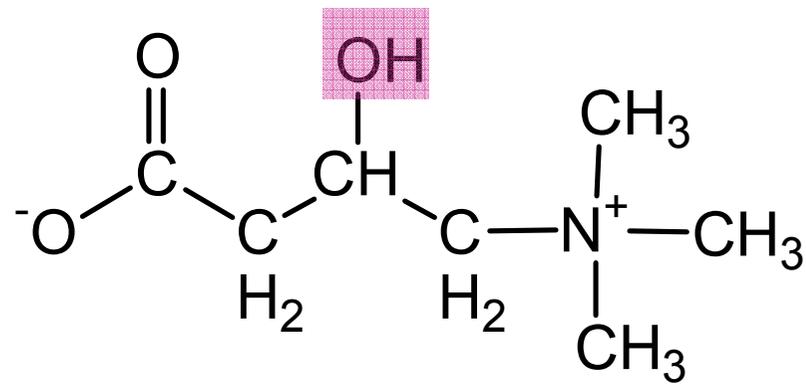
AcilCoA sintetasi

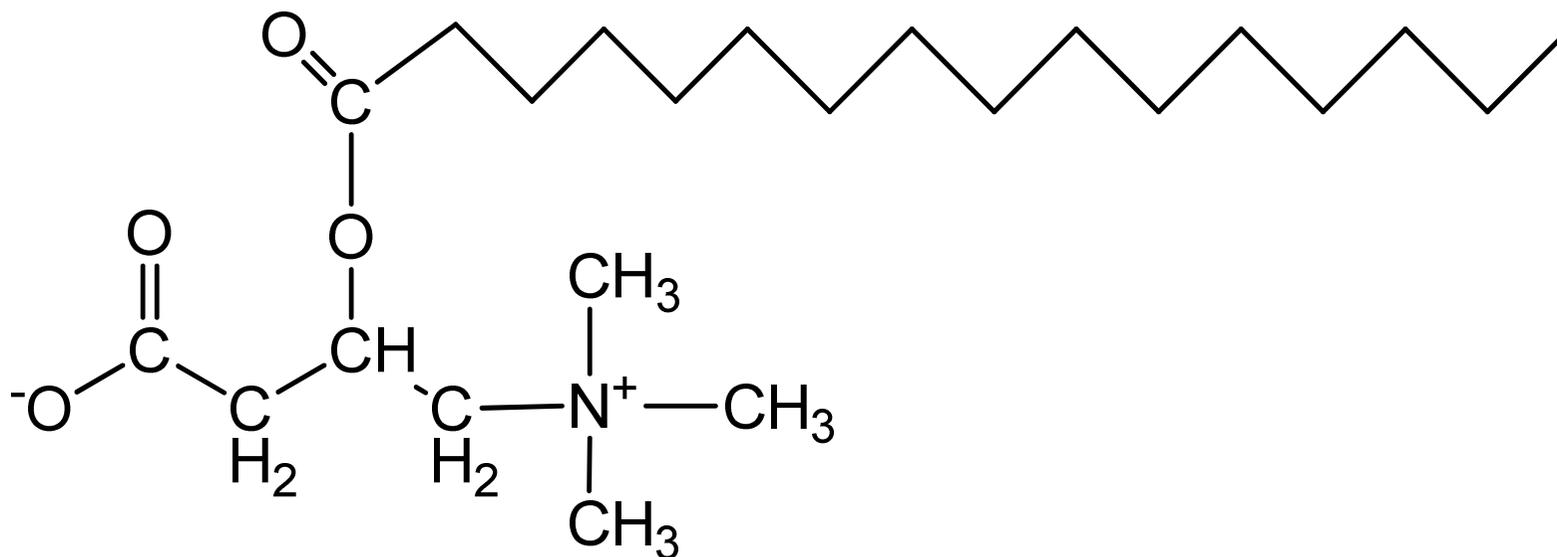
AMP



Acil-CoA

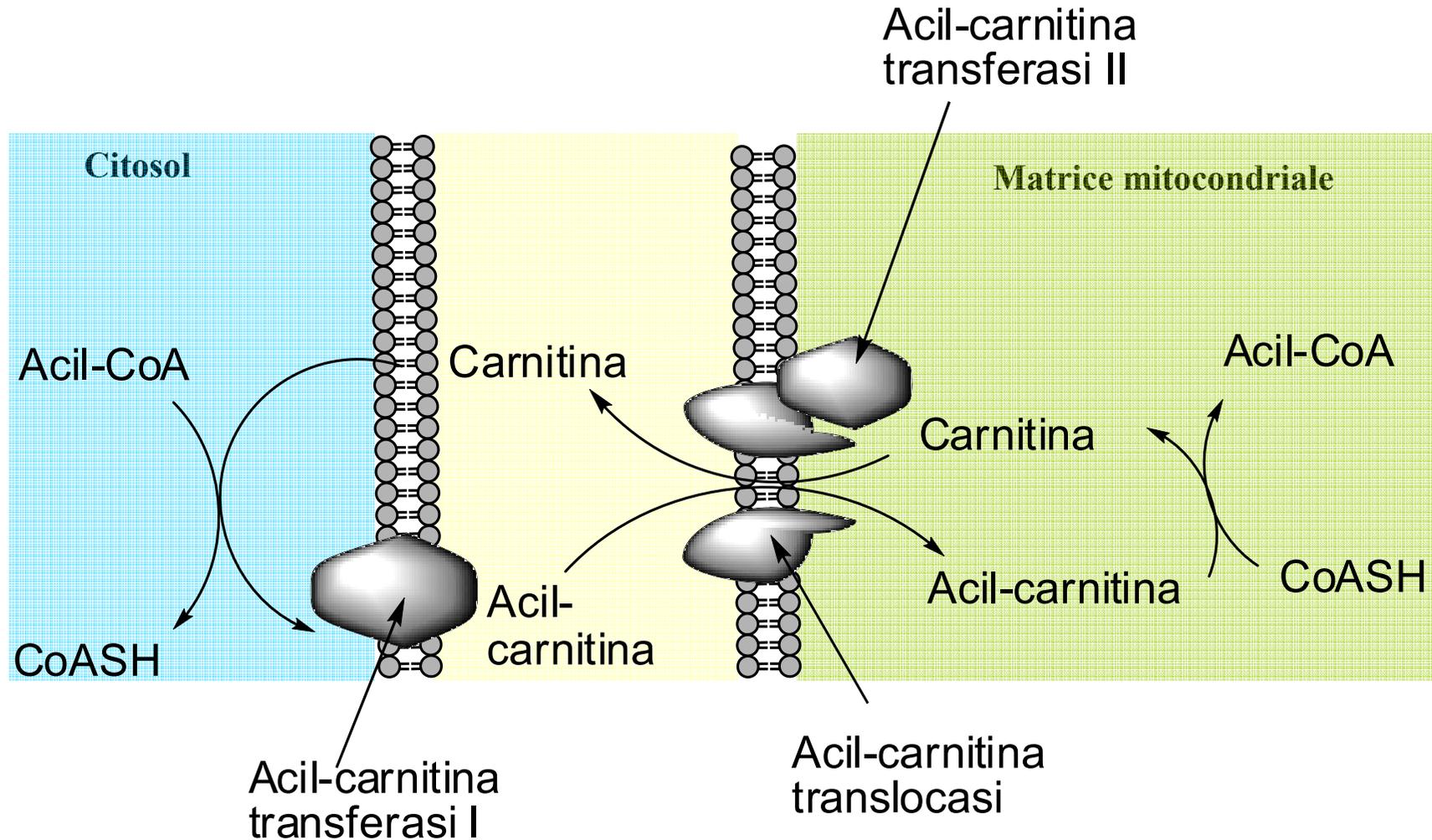
L' aminoacido carnitina





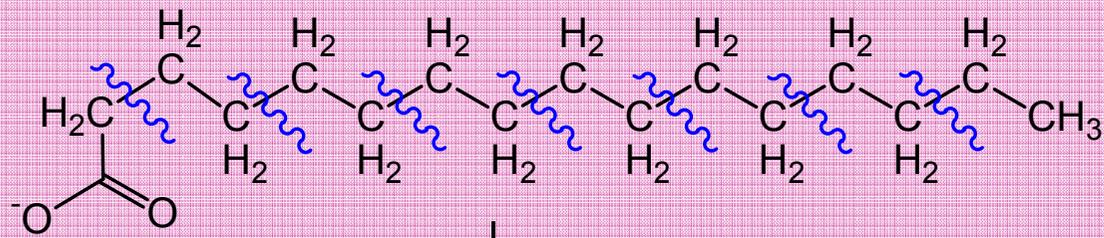
Acil-carnitina

Trasferimento dell'acile all'interno del mitocondrio mediato dalla carnitina



Gli enzimi acil-carnitina transferasi trasferiscono l'acile dal coenzima-A alla carnitina e viceversa;

acil-carnitina traslocasi è un uniporto per l'acil-carnitina.



1a. fase:
β-ossidazione

8 Acetil-CoA

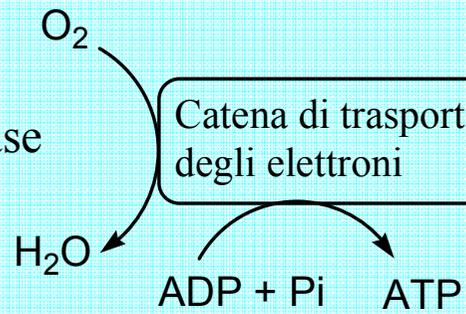
2a. fase

Ciclo di
Krebs

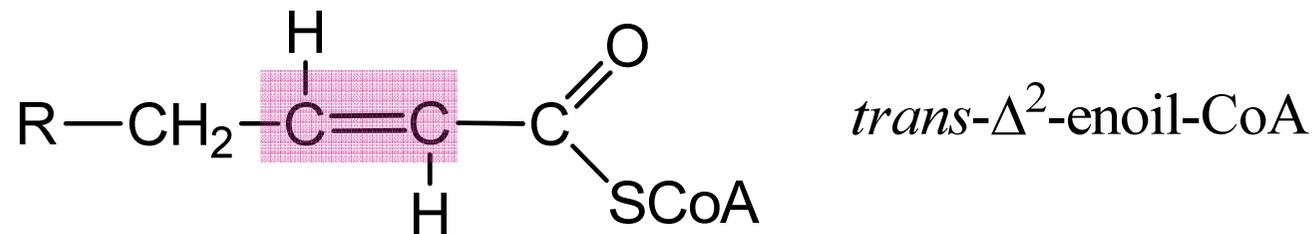
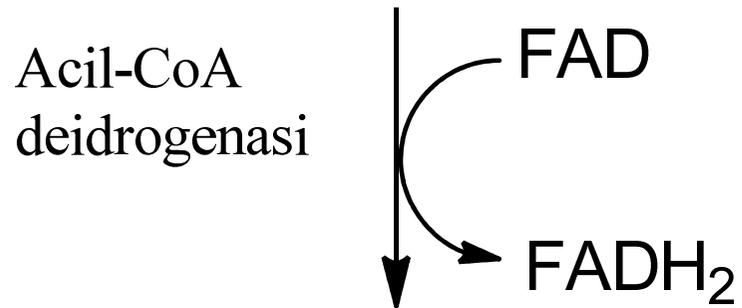
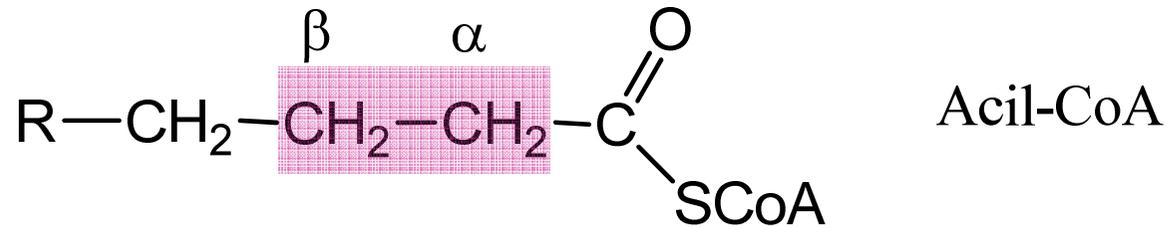
3a. fase

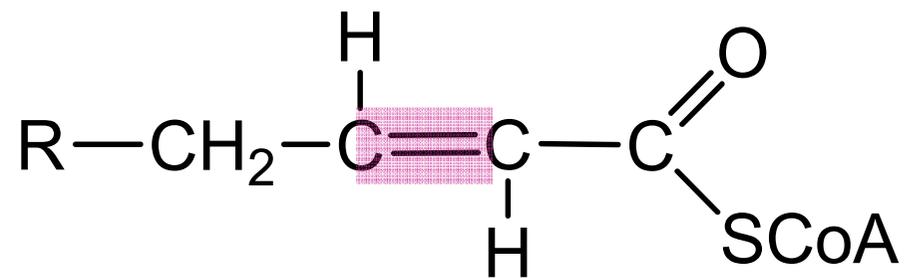
Catena di trasporto
degli elettroni

NADH, FADH₂



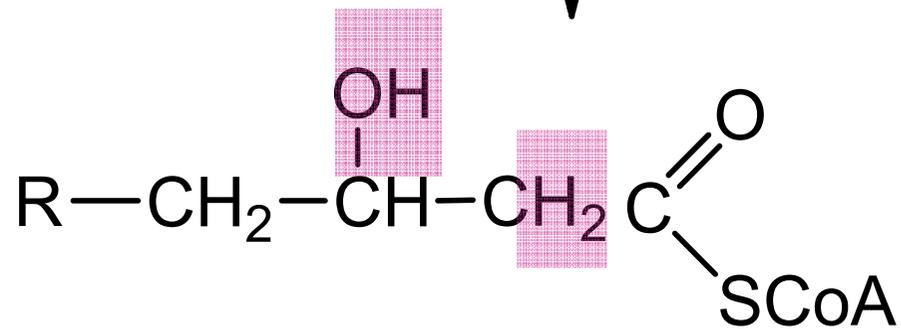
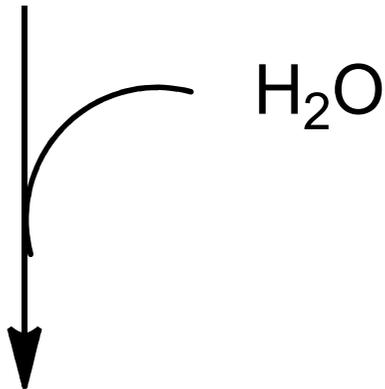
β -ossidazione



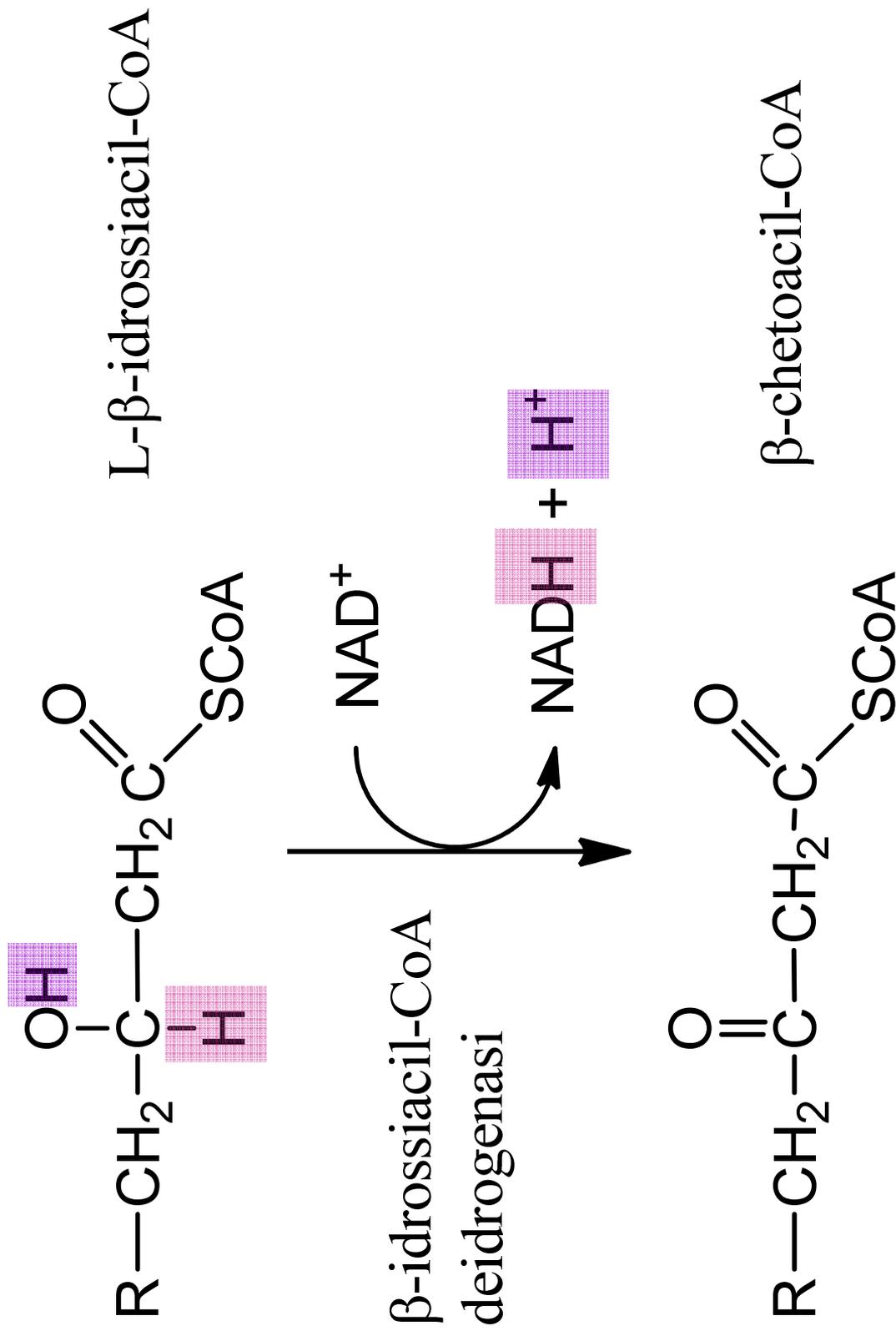


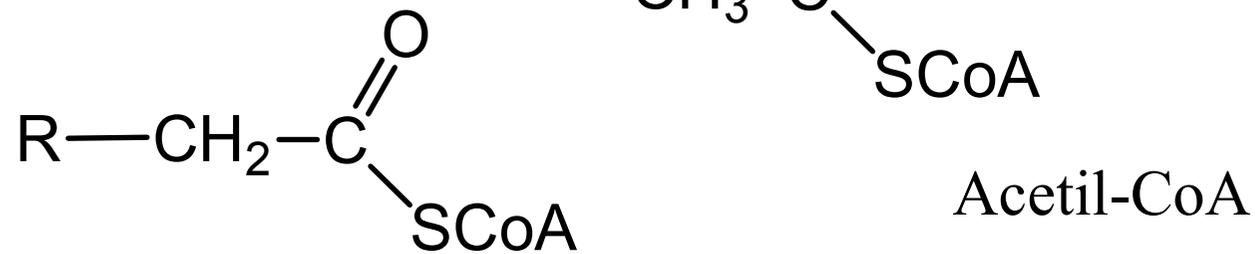
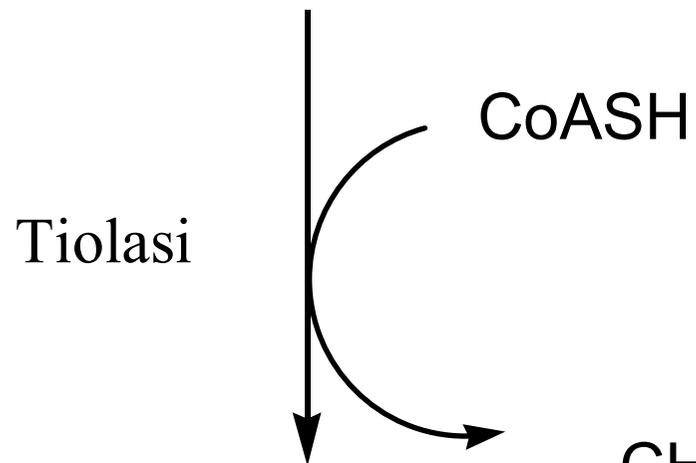
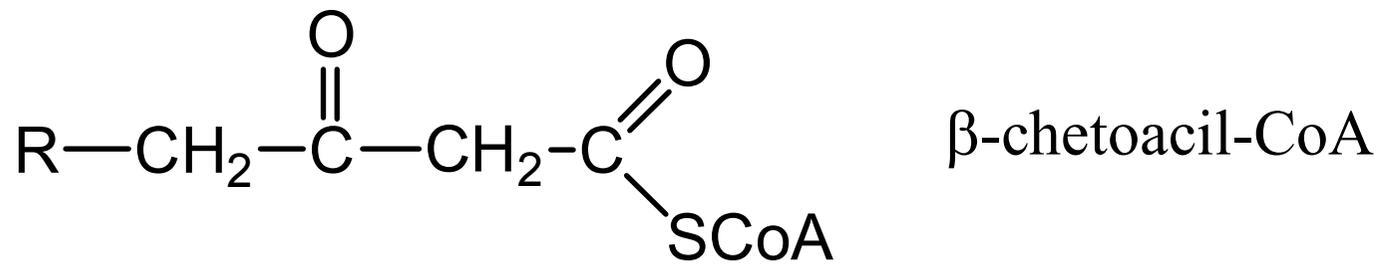
trans- Δ^2 -enoil-CoA

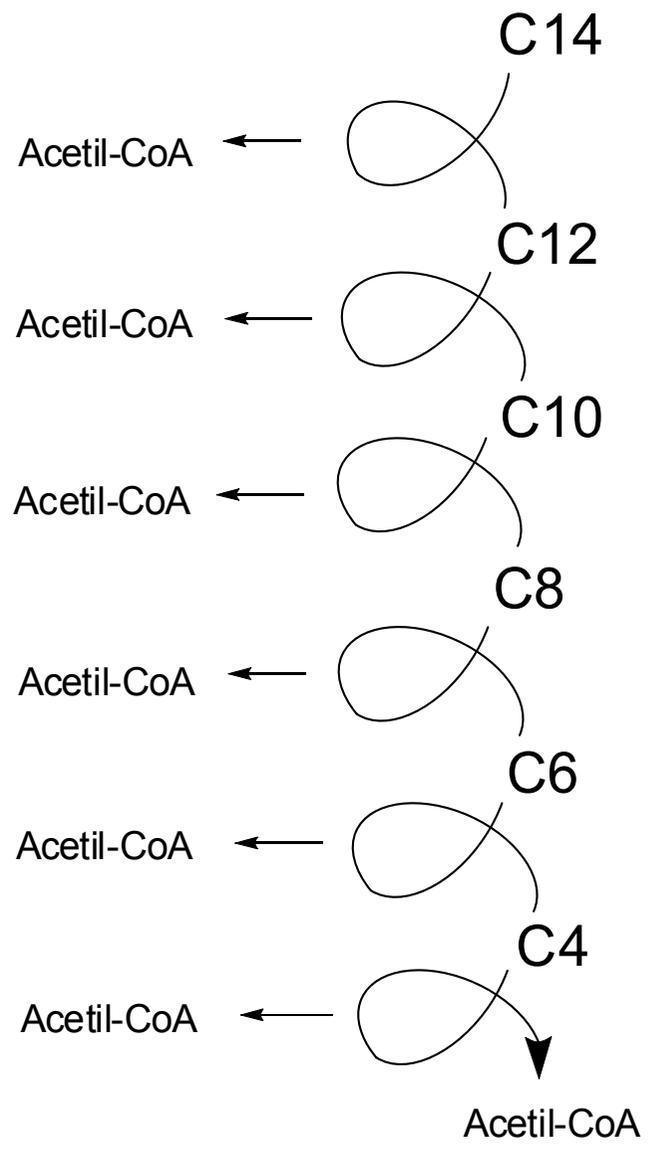
Enoil-CoA
idratasi



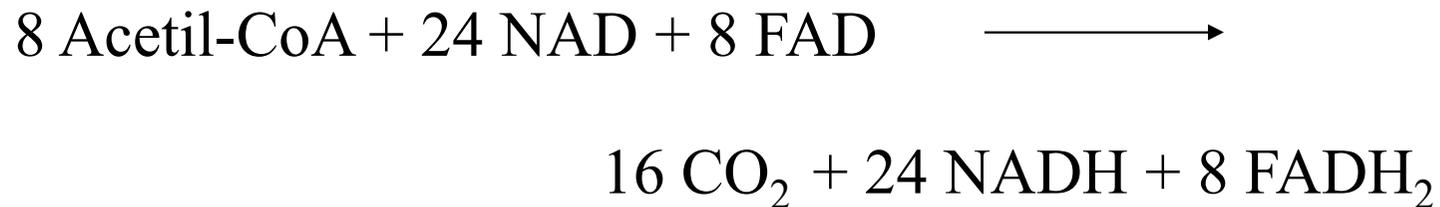
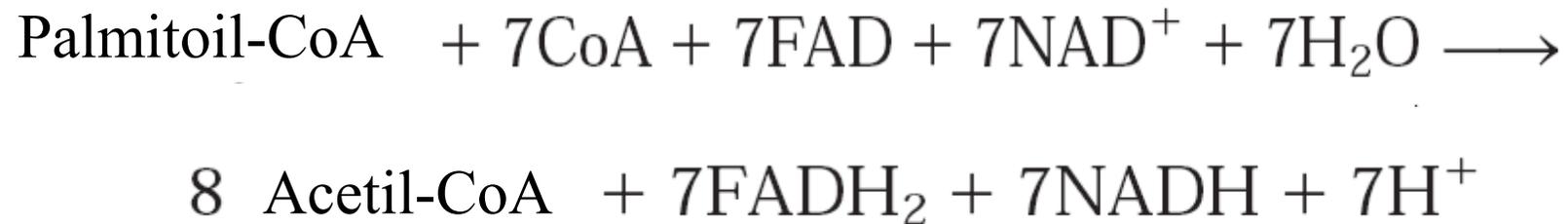
L- β -idrossiacil-CoA







β -ossidazione. Bilancio



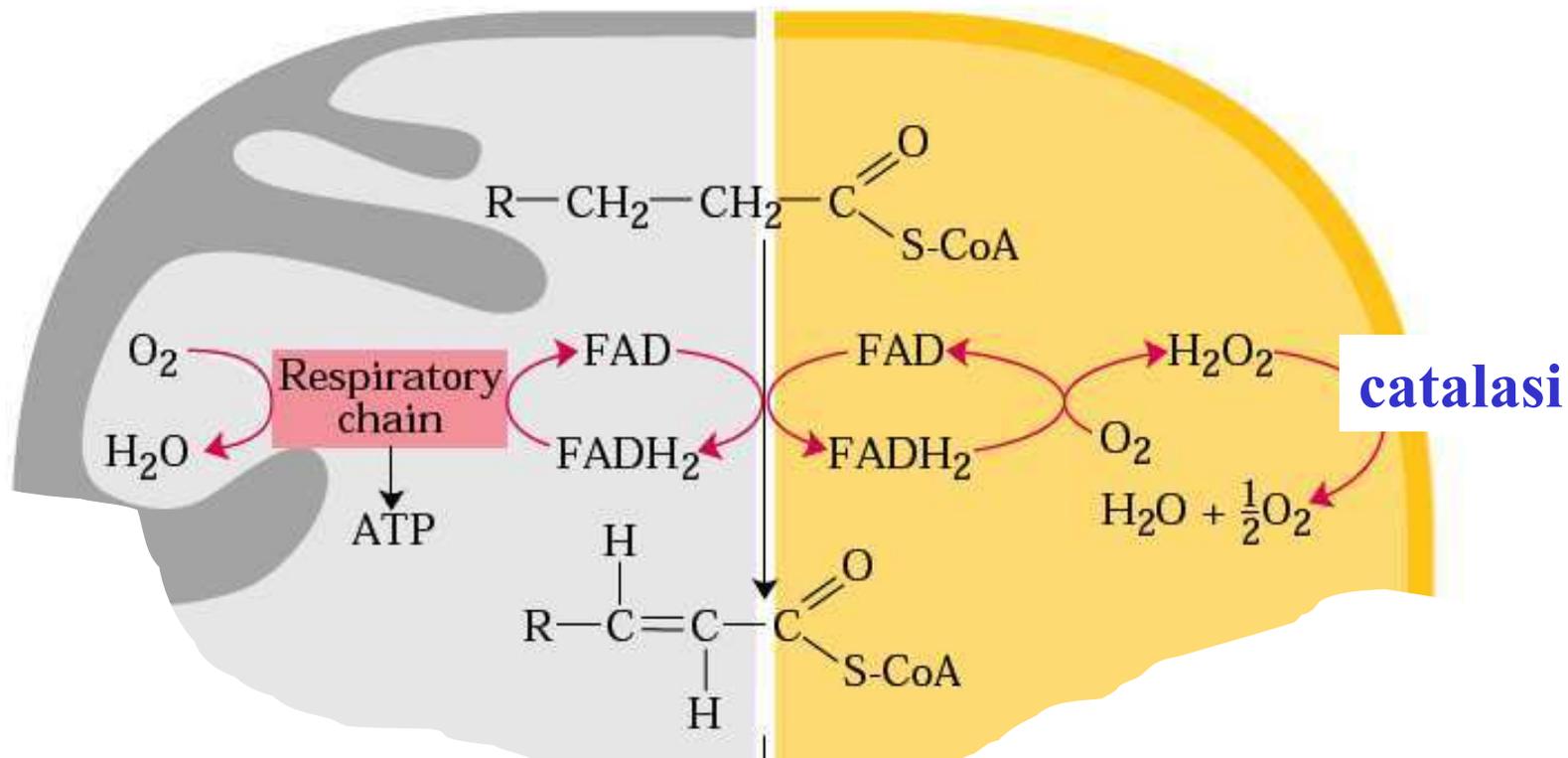


Durante il letargo l'orso ricava l'energia dalla demolizione di grandi quantità di trigliceridi accumulati nella fase estiva

La beta-ossidazione non avviene solo nei mitocondri

Mitocondri:
acidi grassi a catena media

Perossisomi: acidi grassi a catena
lunga; gliossisomi nei semi



qui il $FADH_2$ si riossida
sulla catena respiratoria

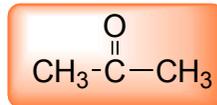
qui la catena respiratoria
non c'è

Se l'acetil-CoA non trova adeguate concentrazioni di ossalacetato si formano i corpi chetonici

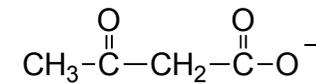
Acetil-CoA

+

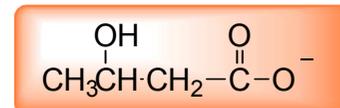
Acetil-CoA



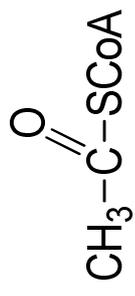
acetone



acetoacetato



b-idrossibutirrato

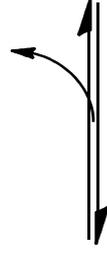


Acetil-CoA

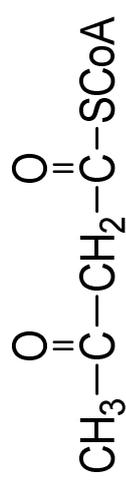


Acetil-CoA

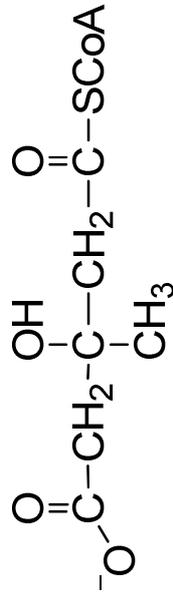
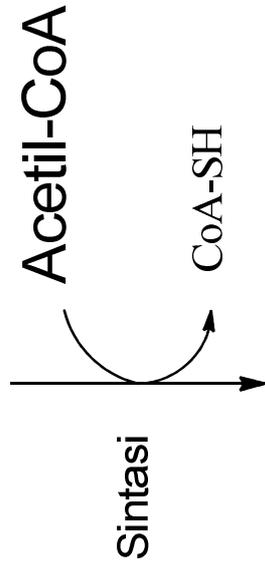
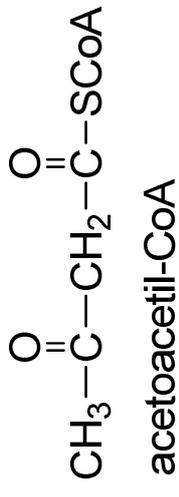
CoA-SH



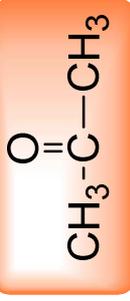
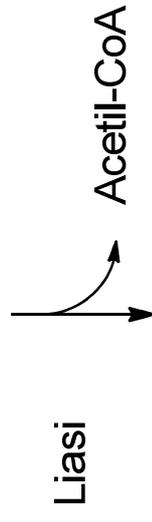
Tiolasi



acetoacetil-CoA

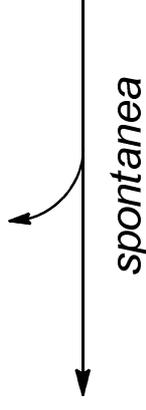


β -idrossi- β -metilglutaril-CoA

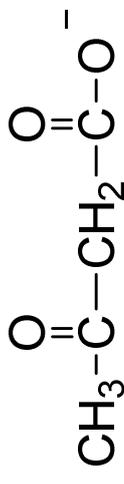


acetone

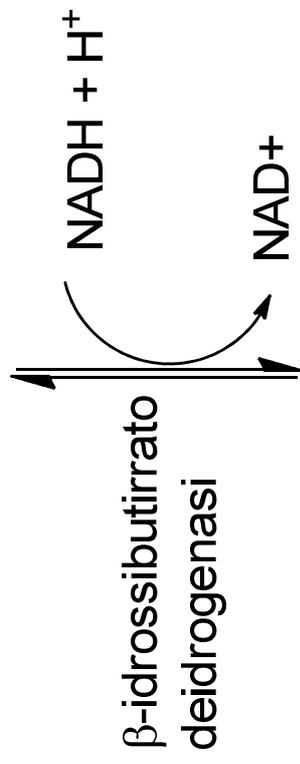
CO₂



acetoacetato



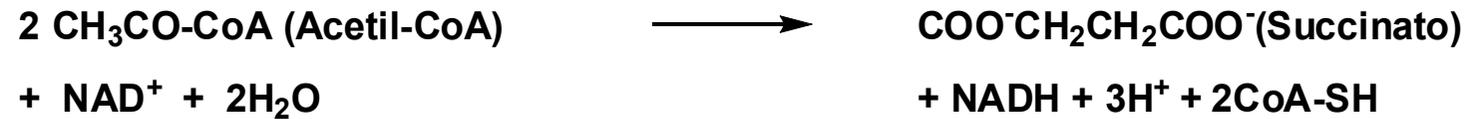
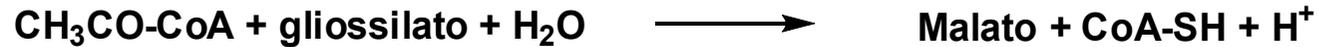
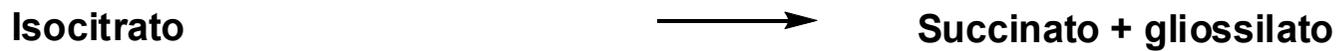
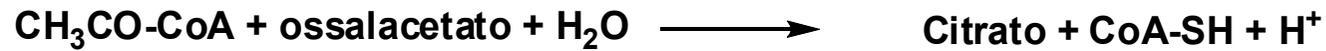
acetoacetato

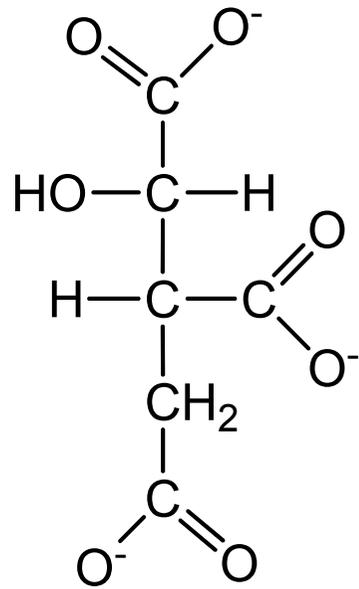


β -idrossibutirrato

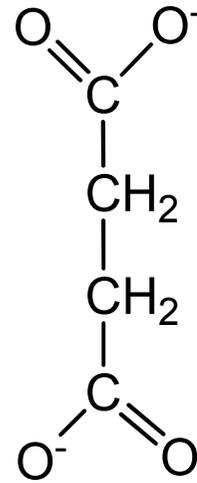
Ciclo del gliossilato

Ciclo del gliossilato. Bilancio

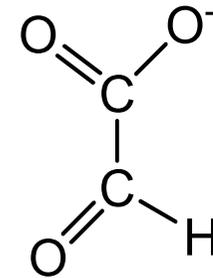




Isocitrato

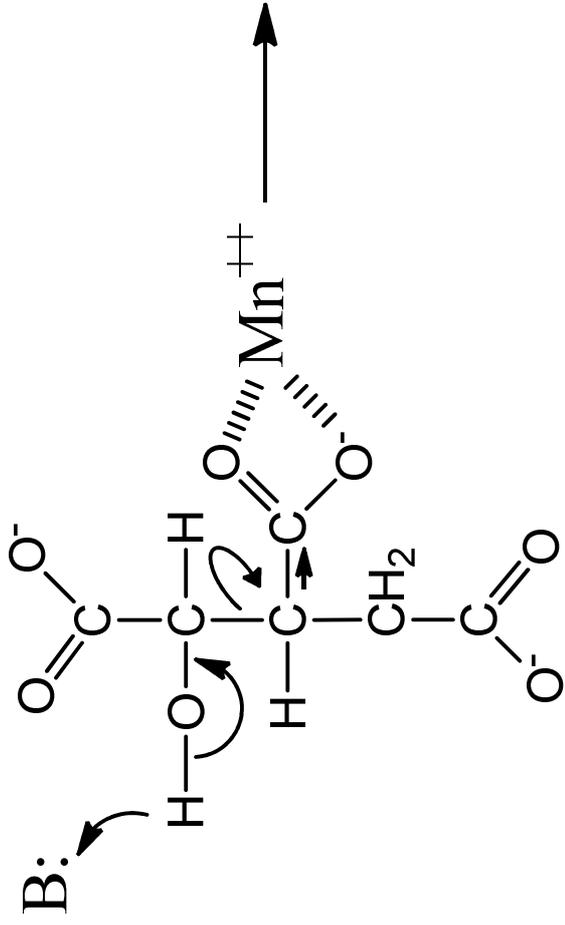
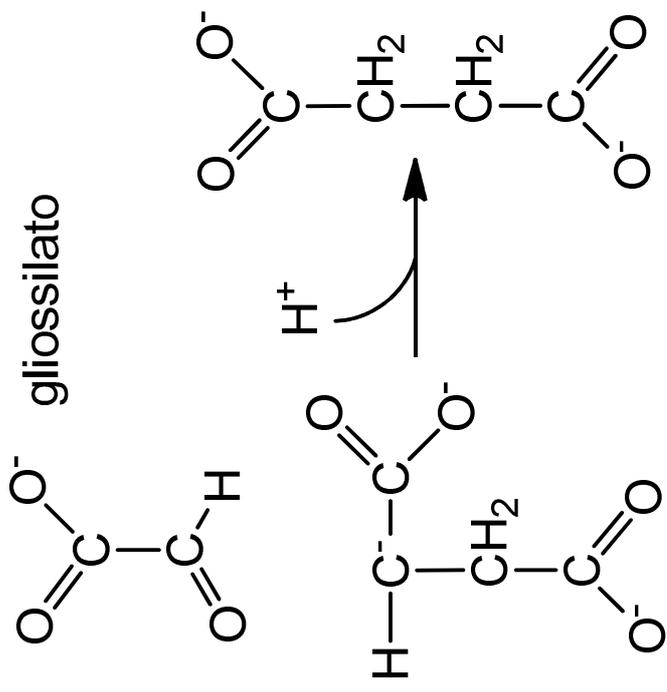


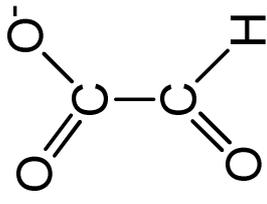
succinato



gliossilato

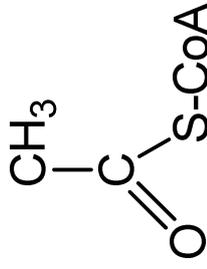
Isocitrato liasi



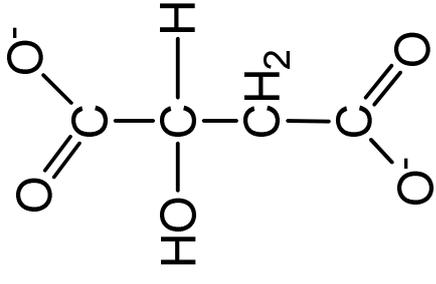
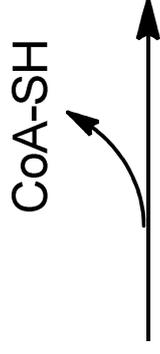


gliossilato

+



acetil-Coenzima A



malato

Malato sintasi

