The metabolic reactions

The study of metabolism has shown, with some exceptions, that most metabolic steps *in vivo* involve one, or a combination, of 5 principal types of simple chemical simple reactions

Major processes :

Oxidation / reduction
<u>Hydrolysis / condensation</u>
Synthesis / braking of C-skeleton

Minor processes:

Cetoenolic tautomery
Hydration / dehydration

(1) The major processes involved in a metabolism can be predicted by looking to the substrate and the final product.

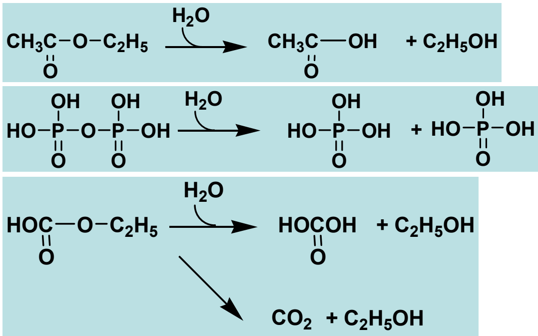
Hydrolysis/condensation

(Transfer reactions)

Hydrolysis condensation

- **Hydrolysis:** reactions involving the braking of a carbon-heteroatom bond (C-N, C-O, C-S…) or a heteroatome-heteroatome bond (O-P, -N-O…).

Exemples



- **Condensation:** reactions involving the formation of carbon-heteroatom bond (C-N, C-O, C-S…) or a heteroatome-heteroatome bond (O-P, -N-O…).

- Hydrolysis reactions are always exergonic ($\Delta G'^\circ <$ O) They are irreversible.

Simple hydrolysis reactions are catalyzed by enzymes called hydrolases.

- Condensation reactions are always endergonic ($\Delta G'^\circ <<$ O) They are impossible.

Condensation reactions are always endergonic. They are impossible and to occur they need to be coupled to other reactions. Most times condensations are coupled to hydrolysis of ATP.

Hydrolysis/condensation coupled reactions are called TRANSFER REACTIONS

Transfer reactions

A big number of condensates exist in life (peptides, sugars, lipids…) the are obtained by condensation reactions coupled to hydrolysis reactions.

Coupled hydrolysis/condensation reactions are called transfer reactions.

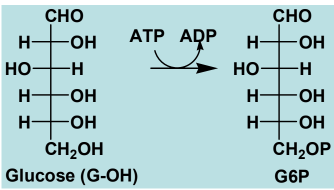
Simple transfer : one hydrolysis coupled to one condensation

Double transfer : two coupled hydrolysis/condensation reactions

Simple transfer (ST)

- ST is a metabolic step involving one hydrolysis and one condensation.
- ST are BiBi reactions: 2 substrates, 2 products. A coenzyme, as ATP, can be considered a one of the substrates.
- ST reactions involve transfer of matter from one substrate to another (for instance a phosphate from ATP).
- The enzymes that catalyze ST are called transferases.
- A ST can be decomposed in a sequence of one hydrolysis and one condensation

Example :



Equivalent

$ATP + H_2O \longrightarrow ADP + P$	Hydrolyse	$\Delta G'^{o} < O$
$GOH + P \longrightarrow G\text{-}OP$	Condensation	$\Delta G'^{o} > O$

In order to make a transfer reaction possible hydrolysis must generate more energy than the condensation reaction.

Double transfer (DT)

- **DT is a metabolic step involving a sequence of 2 ST. The first ST generally involves the hydrolysis of ATP (considered as one of the substrates).**
- **DT are TriTri reactions (3 substrates, 3 products).**
- **DT reactions does not involve transfer of matter.**
- **DT reactions have a common intermediate between the two ST.**
- **The enzymes that catalyze DT are called ligases.**

Example :

$$RCOO^- + HSCoA \xrightarrow{ATP \rightarrow AMP + PP} RCOSCoA$$

Equivalente à

$$\begin{cases} ATP + H_2O \longrightarrow AMP + PP & \text{Hydrolyse} \quad \Delta G'^{\circ} < 0 \\ RCOO^- + HSCoA \longrightarrow RCOSCoA & \text{Condensation} \quad \Delta G'^{\circ} > 0 \end{cases}$$

Observation : DT generally involves hydrolysis of ATP, or another nucleoside triphosphate, as energy donor (ATP gives ADP+Pi) or acceptor (ADP+Pi gives ATP).

DT mechanism

$$RCOO^- + HSCoA \xrightarrow{ATP \rightarrow AMP + PP} RCOSCoA$$

A DT is a sequence of two ST, the common intermediary keeps immobilized to the enzyme by week linkages. In this example the common intermediate common to the two ST is represented :

$$RCOO^- \xrightarrow{ATP \rightarrow PP} [RCOAMP] \xrightarrow{HSCoA \rightarrow AMP} RCOSCoA$$

Fixed to the ligase

The common intermediate can be identified by writing the logic suite of the two ST.

The first ST will always involve the hydrolysis of ATP followed by the transfer of the hydrolyzed monophosphate, or monophosphate-carrying species, to the second substrate (here $RCOO^-$).

Transfer reactions

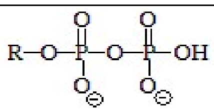
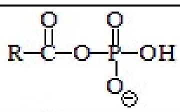
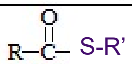
- **The chemical functions involving C-heteroatome or heteroatome-heteroatome (condensates) require | ΔG'°| between 2 and 35 kJ for their hydrolysis *(1)*.**

These chemical functions can be divided in two groups (2):

- Functions of high energy : 25kJ < |ΔG'°| < 35 kJ
- Functions of low energy : 2kJ < |ΔG'°| < 15 kJ

(1) *In vivo,* they vary around 60 kJ
(2) There are exceptions.

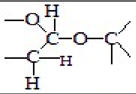
High energy functions

FUNCTION		Hydrolysat	ΔG'° kj (Valeur moy.)	EXAMPLE
Diphosphate		Phosphate	30	ATP…
Acylphosp.		Carboxylate + Phosphate	35	1-3P glycérate
Thioester		Carboxylate + Thiol	30	Acyl-CoA, Succinyl-CoA

It is important to know the functions of high energy but not their ΔG'° value

NB : Phosphoenol pyruvate (PEP) (an intermediate in glycolysis) has a condensation energy of 60 kJ (as 2 ATP). Indeed, PEP accumulates the ATP hydrolysis energy and the energy of a ceto-enolic tautomery .

Low energy functions

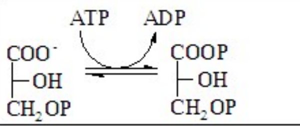
FUNCTION		Hydrolysat	Δ G'° kj (Valeur moy.)	EXAMPLE
Ester	$R-CH_2-C(=O)-O-R'$	Carboxylate + Alcool	14	Glycérides
Ester phosphorique	$R-CH_2-O-P(=O)(O^-)-OH$	Phosphate + Alcool	15	Oses P
Acétale		Oxo + Alcool	15	Osides
Amide	$R-CH_2-C(=O)-NH-R'$	Carboxylate + Amine	3 à 10	Glutamine Liaison pept.
Imines	$>C=N-$	Oxo + Amine	0	Intermédiaires de méc. enz. Ex : Transaminases

It is important to know the functions of low energy but not their ΔG'° value

Transfer between high energy functions

- **Transfers between high energy functions are reversible**
  - **ATP hydrolysis in ADP and P can be used to form a high energy function and inversely, the hydrolysis of a high energy function can afford ATP from ADP and P (1).**

Examples of transfers allowing ATP, ADP or AMP synthesis

FUNCTION	EXAMPLES OF ENZYMES	REACTION
Diphosphate	ATP, AMP kinase ATP, GDP kinase	ATP + AMP ⇔ 2 ADP
Acylphosphate	3P glycérate kinase	
Acyl-CoA	Acyl-CoA ligase Succinyl-CoA ligase	$RCOO^- + CoASH \rightleftharpoons RCOSCoA$ (ATP → AMP + PP)

(1) It is possible to form, in a irreversible manner, a high energy function from the hydrolysis of ATP in AMP and PP.

Transfer from a high energy functions to a low energy function

- Hydrolysis of a high energy function can afford the energy to synthesize a low energy function. The reaction is irreversible.
- Thus, hydrolysis of ATP into ADP + P can give the energy to form a low energy function. ATP will then be the required coenzyme for this condensation.
- However, it is impossible to hydrolyze a low energy function to form AT from ADP + P (1).

Examples of ST and DT forming low energy functions through ATP hydrolysis

FUNCTION	EXAMPLE	REACTION
Ester phosphor.	Glucokinase	GOH +ATP → GOP + ADP
Ester	Acétylcholine ligase	Acétate + Choline → Acétylcholine (ATP → ADP + P)
Amide	Synthèse des dipeptides	$RCOO^-$ → RCOOP (ATP → ADP) → RCONHR' (RNH_2 → P)

ATP or other nucleosides as energy supplier

- When possible, organisms use high energy functions carrying substrates to afford energy for transfer reactions.
- If not possible, organism use ATP as energy source.
- Generally, ATP is hydrolyzed into ADP and P :
  - $ATP + H_2O \rightarrow ADP + P \quad \Delta G'^{\circ} = -30$ kJ
- If the reaction require a mot of energy, ATP can be hydrolyzed into AMP and pyrophosphate (PP). An independent hydrolase decompose PP into 2 P :
  - $ATP + H_2O \rightarrow AMP + PP \quad \Delta G'^{\circ} = -30$ kJ
  - $PP + H_2O \rightarrow 2P \quad \Delta G'^{\circ} = -30$ kJ
- Globally this reaction affords 60 kJ :
  - $ATP + 2\,H_2O \rightarrow AMP + 2\,P \quad \Delta G'^{\circ} = -60$ kJ
- Some times, other triphosphated nucleotides are the energy source (GTP, UTP)
  - Ex : $XTP + H_2O \rightarrow XDP + P \quad \Delta G'^{\circ} = -30$ kJ (jamais en XMP)
- Kinases are enzymes of the transferases family that afford ADP or XTP from ATP :
  - Ex : XDP + ATP → XTP + ADP

Other coupled reactions

In general, all metabolisms use a reduced number of simple reaction, in reality most reactions in life are coupled reactions, as:

- **Simple and double transfer reaction (hydrolysis condensation coupled)**
- **Hydrolysis/reduction**
- **Condensation/oxidation**
- **C-skeleton brake/oxidation**

- ***We will identify some others.***