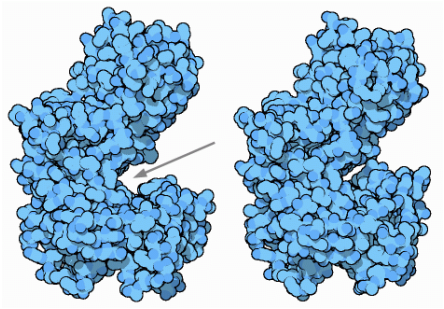
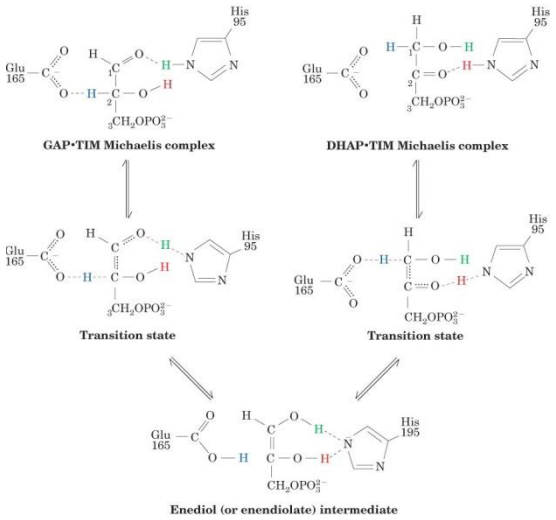
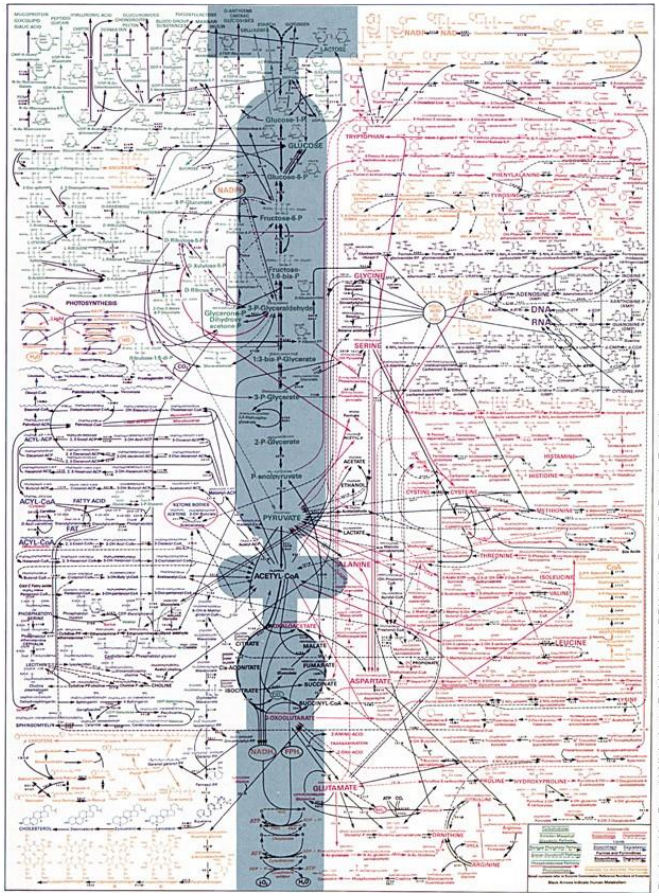
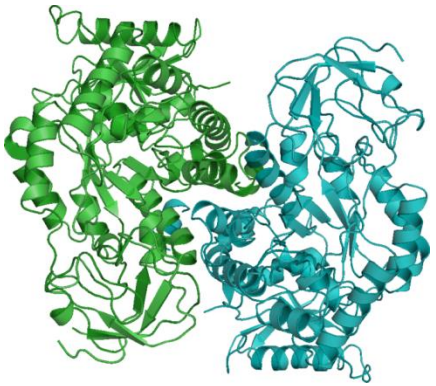
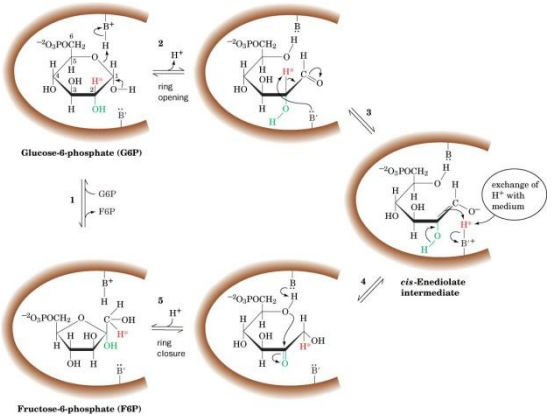
Welcome to Biochem 3050 / Biology 3010: Enzymes and Metabolism











Course Director: Derek J. Wilson

The Syllabus 2024

York University
Department of Chemistry and Department of Biology

Advanced Biochemistry, Winter 2024
Biology 3010 3.0 / Chemistry 3050 3.0 / Biochemistry 3010 3.0

Instructor: Derek Wilson
Office: LSB331C
email: dkwilson@yorku.ca

Lectures: **M/W/F 9:30 – 10:30**
M/W/F Steadman Lecture Hall D

Office Hours: Monday, Wednesday, and Friday 10:30-11:30 LSB331C

Prerequisites: SC/BIOL 2020 4.0 or BCHM 2020 4.0 or SC/CHEM 2050 and SC/CHEM 2020 6.0.

Calendar Description: A detailed discussion of enzyme structure and function. The chemistry and metabolism of biological molecules. Metabolic regulation at the level of enzyme activity. Knowledge of general concepts of metabolism and of basic aspects of enzyme structure and function is assumed.

Text*: I recommend '*Biochemistry*' Donald Voet and Judith Voet, any edition, John Wiley & Sons, Inc. publishers.
* This text is recommended, but **not** required. *Almost All* of the material will be available in any recent, university level biochemistry text and in the (online) lecture notes.

Library Material: A number of biochemistry textbooks are on reserve in the Steacie Library including…
Lehninger Principles of Biochemistry. Nelson & Cox.
Biochemical Calculations, Segel.
Biochemistry, Horton, Moran, *et al*.
Biochemistry, Stryer.
Introduction to Protein Structure, Branden & Tooze.

Website: Course material can be accessed by linking from http://www.yorku.ca/dkwilson. All documents pertaining to the course will be posted.

Marking scheme:
Midterm exam 1 - 30% February 16th
Midterm exam 2 - 30% March 22rd
Final exam - 40%

Grading: The grading scheme for the course conforms to the 9-point grading system used in undergraduate programs at York (e.g. A+=9, A=8, B+=7, B=6, C+=5, C=4, D+=3, D=2, E=1, F=0). A letter grade for the course will be assigned based on the final percentage grade (A+=90-100, A=80-89, B+=75-79, B=70-74, C+=65-69, C=60-64, D+=55-59, D=50-54, E=40-49, F=0-39).

Academic Honesty:
York students are required to maintain high standards of academic integrity and are subject to the **Senate Policy on Academic Honesty**:
(https://www.yorku.ca/secretariat/policies/policies/academic-honesty-senate-policy-on/)

Students may also review York's 'SPARK' materials on the **Academic Integrity**:
(https://spark.library.yorku.ca/academic-integrity-what-is-academic-integrity/)

Access/Disability: Students with disabilities, including physical, medical, systemic, learning and psychiatric disabilities may need accommodation in exam requirements. Students are encouraged to notify the course director and to seek advice from the Counselling and Development Centre. Failure to notify the course director of your needs in a timely manner may jeopardize the opportunity to arrange for academic accommodation.

Notes:
(1) ***E-mail policy.*** All emails must include the name of the sender. It is preferred that your@yorku.ca email address be used. Messages from accounts like bleh@hotmail.com or similar may not receive a reply, probably because the email will be sent to my spam box.

(2) ***Test Marking***: Test grades are normalized to test difficulty by 'bumping' the entire class by an amount that makes the highest grade 100% (***i.e.***, if the highest grade is a 98%, then everyone's grade will be increased by 2%).

(3) ***Missed tests and exams:*** There **may or may-not** be a make-up for missed midterm tests/exams. If not, for each missed midterm (with appropriate documentation) the value of the test will be added to the remaining midterm and final exam (for a missed midterm exam 1) or to the final exam (for a missed midterm exam 2).

(4) ***Re-grade policy***. If, after tests are graded and returned, there is a question concerning the grading of a test, the *entire* test should be returned. The *entire* test may then be re-graded. All requests for re-grading must be made in writing and must be submitted to Dr. Wilson no later than the end of lecture 1 week after the test is returned to the class. The request should identify the question of concern and briefly explain the marking error and/or scientific reason why your answer merits further consideration.

The Syllabus 2024

Course Outline (Approximate!!)

Week 1 (Jan 8th - 12th): *Introduction. What is this thing called 'metabolism'? WHY??*

Week 2 (Jan 15th - 19th): *Proteins – Amino acids to Peptides to Proteins*

Week 3 (Jan 22nd – 26th): *Enzymes and Protein Structure*

Week 4 (Jan 29th – Feb 2nd): *Enzyme Regulation and Mechanisms – Kinetics and Thermodynamics*

Week 5 (Feb 5th – 9th): *Enzyme Regulation, Enzyme dynamics and Function*

Week 6 (**Feb 12th – 16th**): *Enzyme Function, Review,* ***Mid-Term!*** *(**Feb 16th**)*

Reading Week (Feb 19th – 23rd)

Week 7 (Feb 26th – March 1st)***:*** *Metabolic Pathways, Enzymes and Energy Metabolism*

Week 8 (March 4th – March 8th): *Metabolism of Fatty Acids*

Week 9 (March 11th – March 15th): *Metabolism of Nucleotides and Amino Acids*

Week 10 (**March 18th – March 22nd**): Metabolism, *Review*, ***Mid Term! (March 22nd)***

Week 11 (March 25th – March 29th): *Metabolism of Iron/Calcium*

Week 12 (April 1st - April 5th): *Metabolism of Caffeine, Metabolic Poisons*

Week 13 (April 8th): *Exam prep*

Extra, maybe!: *Evolution of Metabolism*

Metabolism – What is it?

Websters – 'the sum of the processes in the buildup and destruction of protoplasm; *specifically* : the chemical changes in living cells by which energy is provided for vital processes and activities and new material is assimilated b: the sum of the processes by which a particular substance is handled in the living body c: the sum of the metabolic activities taking place in a particular environment ‹the *metabolism* of a lake›'

Websters Etimology - International Scientific Vocabulary, from Greek metabolē change, from *metaballein* to change, from meta- + *ballein* to throw — **more at devil**

?

Wikipedia – Metabolism is the set of chemical reactions that occur in living organisms in order to maintain life

Metabolism Allows:

- Collection/Storage of Energy
- Maintenance of pH, temperature, salt conditions
- Fabrication of big, low entropy molecules

Metabolsim – Why?

Big Questions

How did metabolism appear? What was the earliest metabolism?

Metabolic networks – where are the weak points and why are they there?

Can metabolic control be reduced to a small number of archetypes?

Applications

- Higher/faster/stronger 

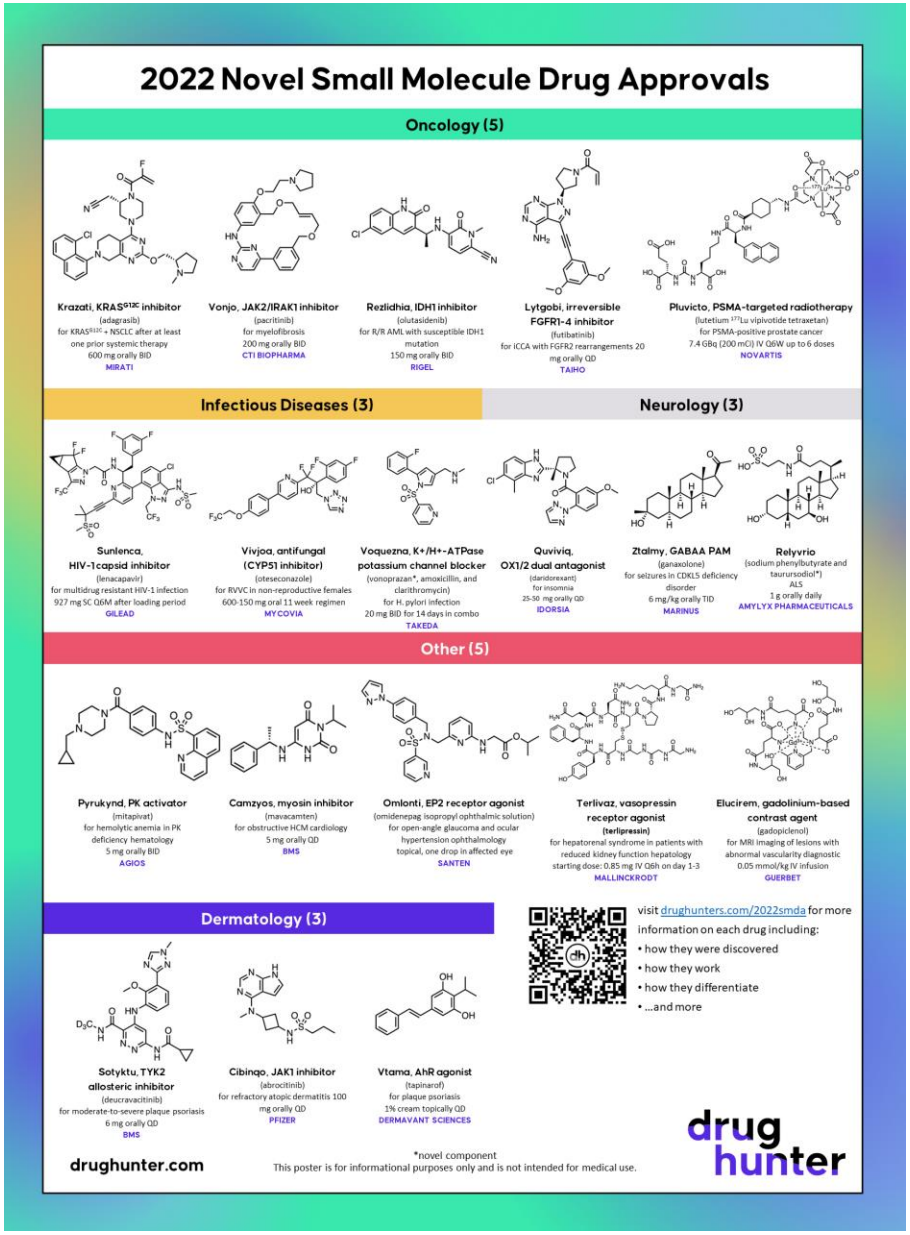
- Metabolic diseases / disorders / syndromes: Diabetes, Wilson's disease, many, many others

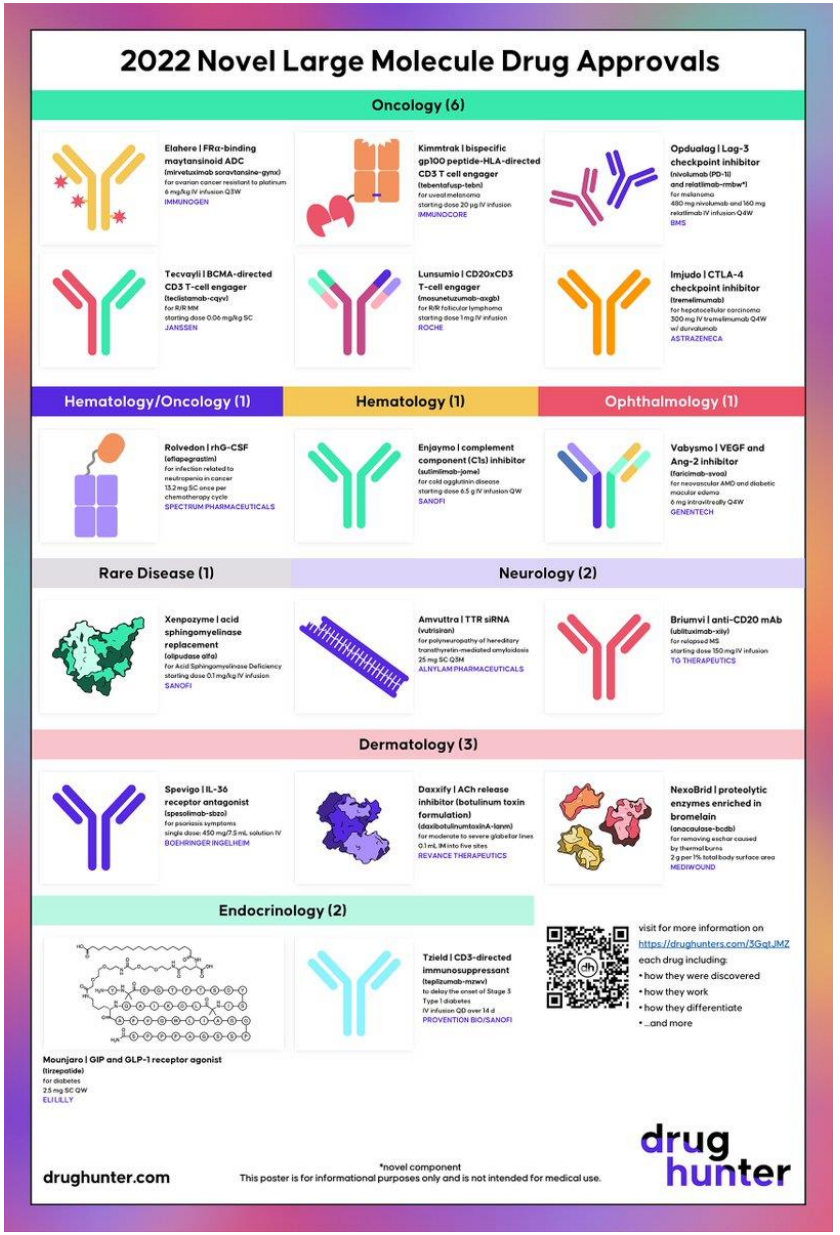
- Metabolic poisons  : Cyanide, 2,4-Dinitrophenol, Oligomycin, many, many others

- ***Drug metabolism***

- Nutrition

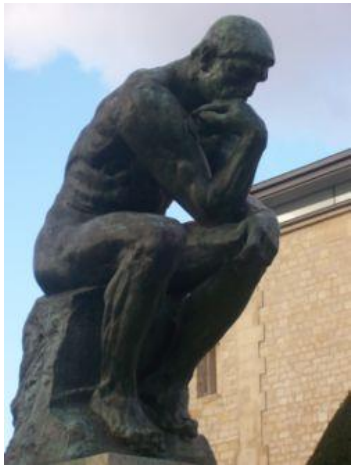
Metabolsim – Why Part Deux





Course Outline

Who started thinking about metabolism first?



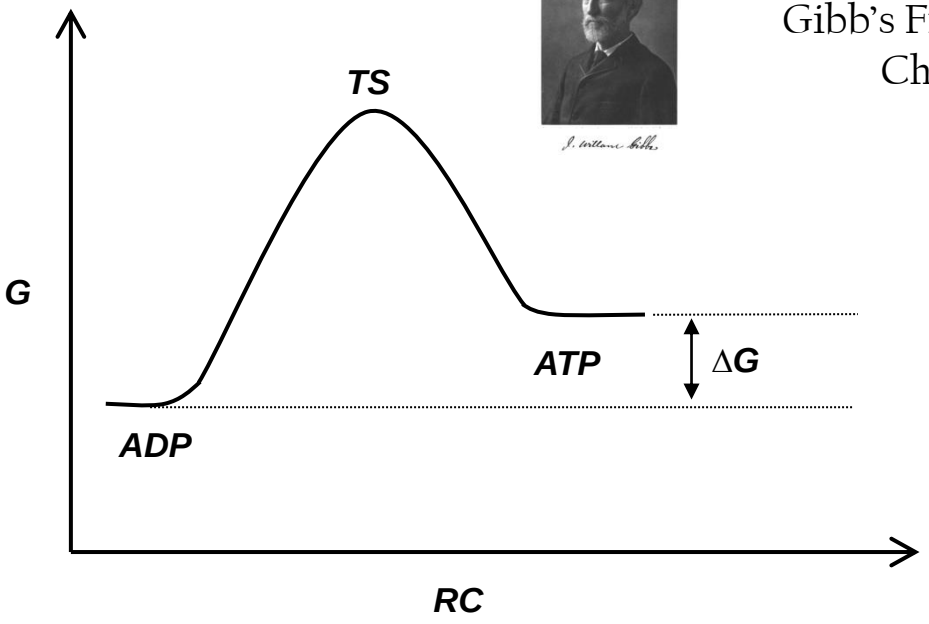
Paris

Washington

Kyoto

Metabolism, Chemically

The Challenge: Most of the Processes Required to Sustain Life are ***Endergonic***



Gibb's Free Energy Change

Enthalpy Change (energy)

Entropy Change (degrees of freedom)

$$\Delta G = \Delta H - T\Delta S$$

-ΔG:  ***Exergonic***: Product is favored

+ΔG:  ***Endergonic***: Product is disfavored

Oxidation of food: ***Exergonic***.

Making new chemical bonds, mechanical work, maintenance of gradients: ***Endergonic***.

Staying alive: **Priceless**.

Gibb's Free Energy and Equilibrium

What this means is that if all the big, complex molecules of life were sitting there, they would ultimately just fall apart...

$$\Delta G^\circ = -RT \ln(K_{eq})$$

For example, the reaction ATP $\rightarrow$ ADP has a ΔG° of -30.5 kJ/mol. So, if I make up a batch of ATP and shake it around, after a **gazillion** years the equilibrium constant (ADP / ATP) will look like...

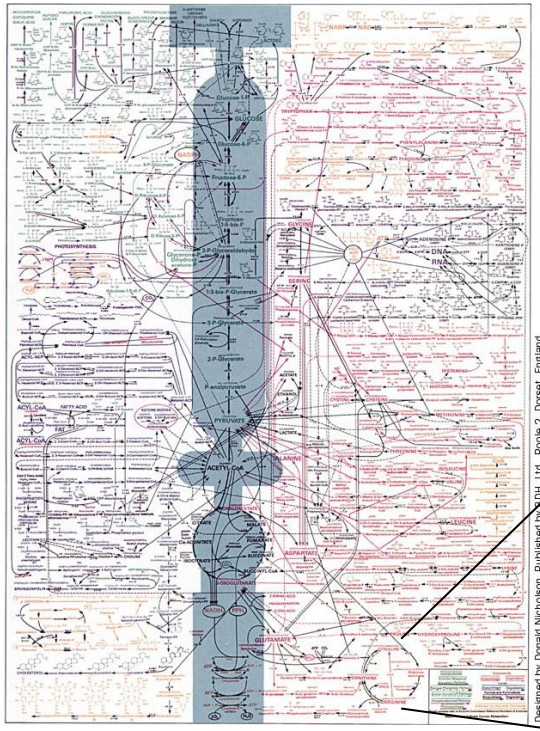
$$K_{eq} = \left(\frac{[ADP]}{[ATP]} \right) = e^{((30.5 kJ/mol)/(.008314 \times 298))} = 2.2 \times 10^5$$

In other words, all but 1/220000th of the ATP has spontaniously decomposed to ADP. Since we need ATP for energy, that is bad.

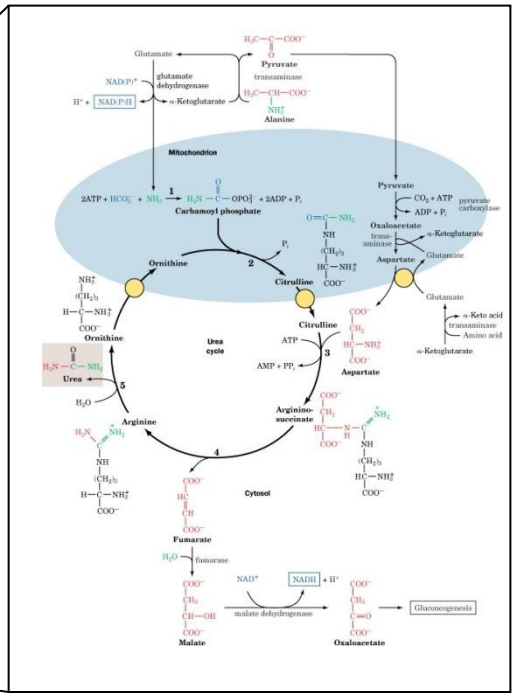
We need a way to get around this problem...

A Solution to the Equilibrium Problem: Metabolic Pathways

- Metabolism is a network of chemical reactions which are almost always mediated by enzymes



- A linked set of reactions within the network is a ***metabolic pathway*** or ***cycle***.



- This allows for '**linked reactions**' where we sortof '**grab**' unfavorable products and put them through a **highly favorable reaction** before they can decompose...

Metabolic Pathways

- In sum, ***pathways*** are almost ***always exergonic***, and very often largely so.

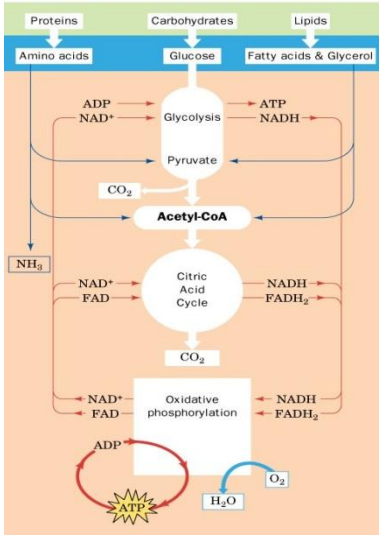
  e.g. from Glucose to Pyruvate is ≈ -130 kcal/mol

- This does not mean that ***all*** reactions in the pathway are exergonic

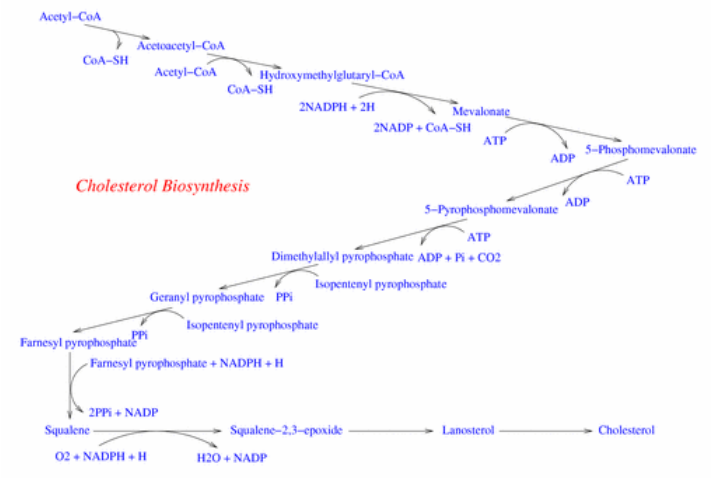
  e.g. from Glucose to Glyceraldehyde-3-Phosphate is ≈ +20 kcal/mol

- Metabolic pathways can be ***Catabolic*** (break stuff down - degradation) or ***Anabolic*** (build stuff up - synthesis)

- ***Catabolic*** pathways start from a range of molecules (carbohydrates, proteins, lipids), converging on a relatively small number of intermediates.



- ***Anabolic*** pathways start from a small number of molecules (*i.e.* pyruvate, Acetyl CoA, citrate) and make a huge variety of products



Regulating Metabolic Pathways

- Control of metabolic pathways is by ***regulating the expression or activity*** of enzymes that catalyze 'committed steps'
    - Regulation of enzyme activity = FAST
    - Regulation of expression = SLOW

- Metabolic processes are ***compartmentalized*** in every organism higher than a Eukaryote

Organelle	Function
Mitochondrion	Citric acid cycle, electron transport and oxidative phosphorylation, fatty acid oxidation, amino acid breakdown
Cytosol	Glycolysis, pentose phosphate pathway, fatty acid biosynthesis, many reactions of gluconeogenesis
Lysosomes	Enzymatic digestion of cell components and ingested matter
Nucleus	DNA replication and transcription, RNA processing
Golgi apparatus	Posttranslational processing of membrane and secretory proteins; formation of plasma membrane and secretory vesicles
Rough endoplasmic reticulum	Synthesis of membrane-bound and secretory proteins
Smooth endoplasmic reticulum	Lipid and steroid biosynthesis
Peroxisomes (glyoxisomes in plants)	Oxidative reactions catalyzed by amino acid oxidases and catalase; glyoxylate cycle reactions in plants

Course Outline

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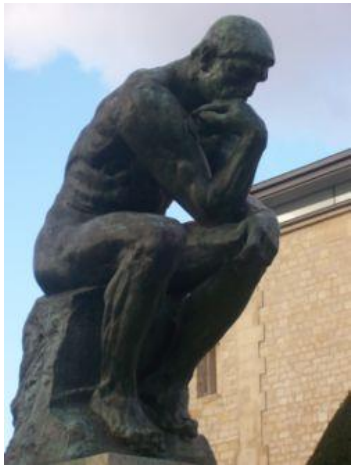


Paris

Washington

Kyoto

Metabolic Research: The 'Pee' Years

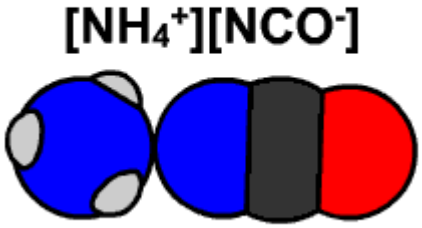
Friedrich Wöehler

Scientists in the early 1800's were aware that differences existed between the chemical reactions of life and plain old boring chemical reactions

Their explanation for this difference?: The '***vital force***' a.k.a the '***internal flame***'

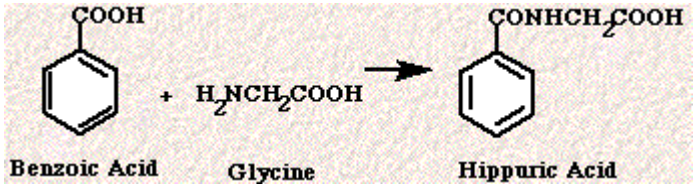
The ***Science*** of metabolism really started when Wöehler (accidentally) synthesized Urea from Ammonium Cyanate

$$NH_4(CNO) \rightarrow NH_3 + HCNO \leftrightarrow (NH_2)_2CO$$



Many of Woehler's experiments were carried out on himself or, if that was too dangerous – his dog!

1841 – First productive human metabolism experiment: ***Alexander Ure*** observes conversion of Benzoic Acid to hippuric acid and proposes Benzoic Acid as a treatment for Gout

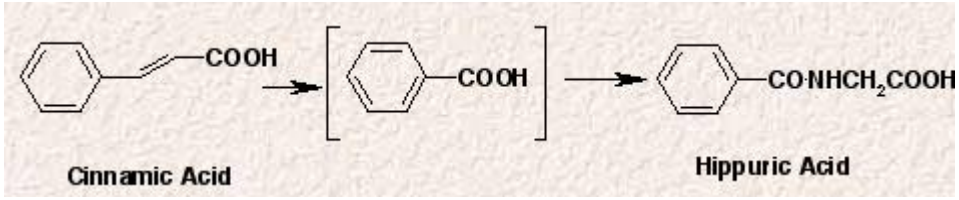


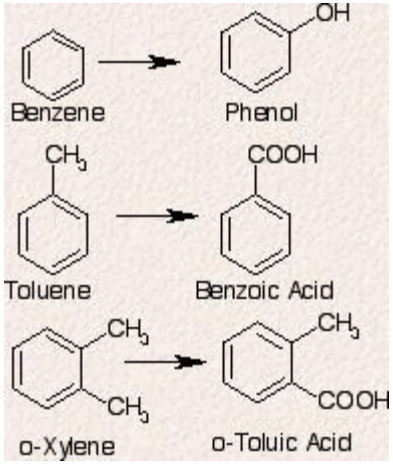
http://www.issx.org/i4a/pages/index.cfm?pageID=3306

More on Understanding Pee

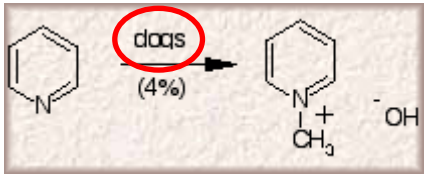
The first strategy of metabolic chemists: 'Feed 'em some phenyl derivative and we'll see what comes out in the urine'. Mid to late 1800's.

Oxidation

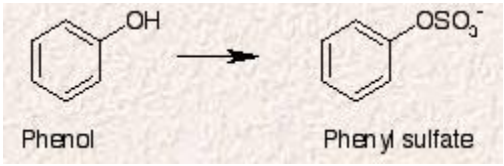


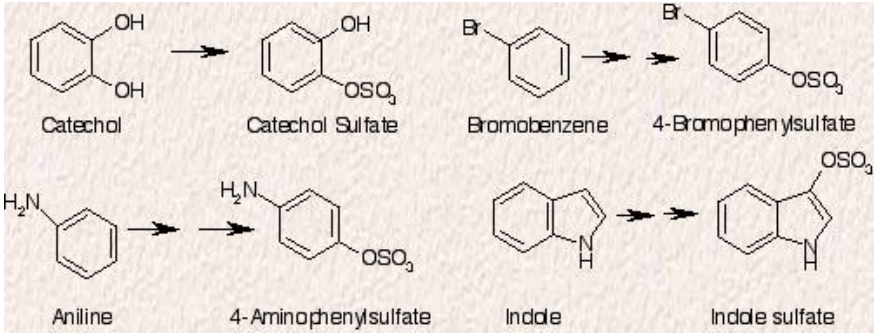


Methylation

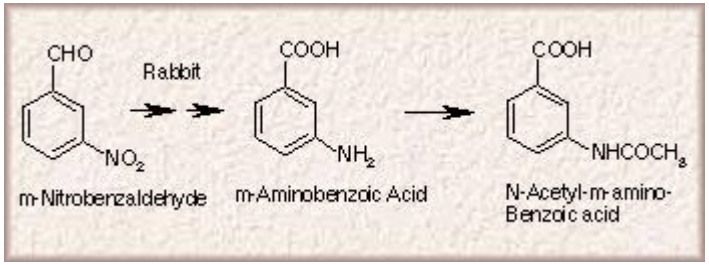


Sulfate Conjugation

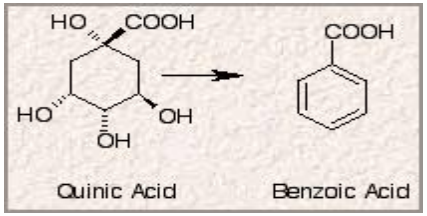




Acetylation

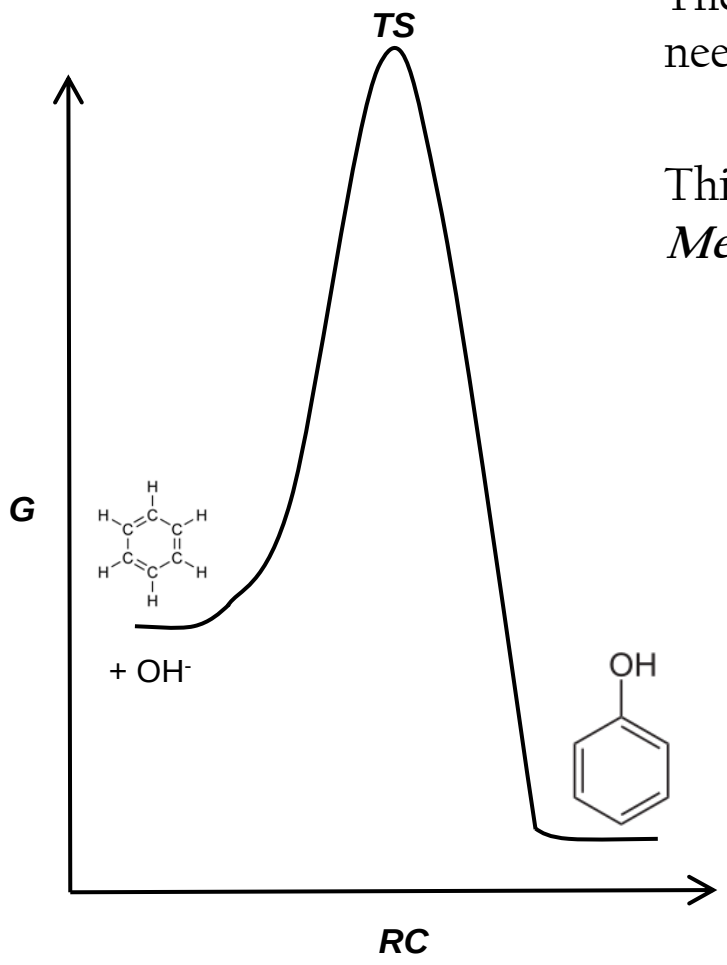


Reduction



Most of these chemistries are **very hard**. The products are ***very stable***, but if you throw in the reactants ***nothing happens***... Hunh?

The Trouble With Making Pee:



The reaction is favorable, but it'll never happen. We need Catalysts!

This is the basis for the connection between ***Metabolism*** and ***Enzymes***.

Note that in this case, even **unstable products** will hang around for quite a while once they are formed, so there's no need to 'grab' them quickly. This is called '**kinetic trapping**' and it's in large part why we are able to hang on to **ATP** once we've made it...

Same Bat-time, Different Bat-channel

Fortunately, at the same time as our metabolic chemists were busy examining pee, **Eduard Buchner** was hard at ***killing yeast***.

Interestingly, he found that ***yeast extract*** could ***still ferment sugar***!

1907

This was actually about ***40 years after*** Payen and Persoz first isolated an enzyme (1833) that could break down starch. We now know and love this enzyme as ***amylase***

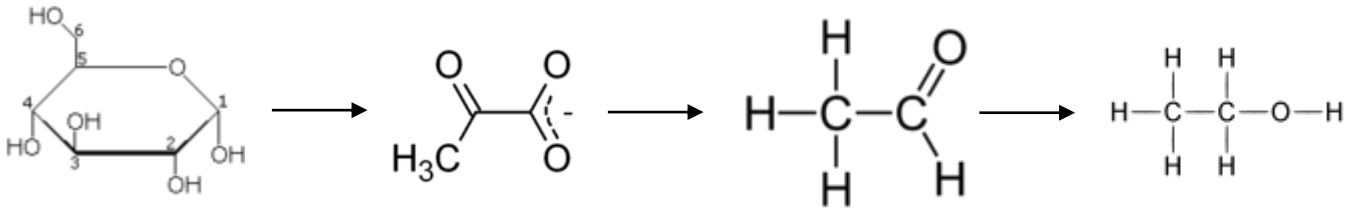
The difference was that Buchner knew he was dealing with proteins, mainly because of the work of this man:

Gerardus Mulder

1802-1880

Egg albumin:

Carbon	400	30,574.80	54.90
Hydrogen	620	3,868.68	6.95
Nitrogen	100	8,851.80	15.89
Oxygen	120	12,000.00	21.55
Phosphorus	1	196.16	0.35
Sulphur	1	201.17	0.36
		55,692.61	100.00

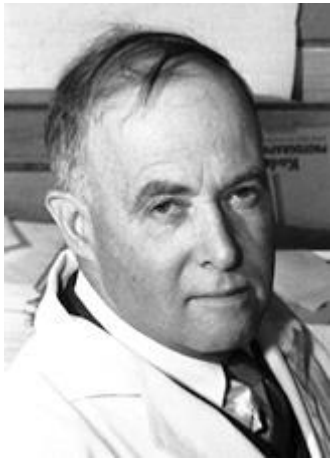


What Are These Things Called Enzymes?

OK, so something non-living and associated with proteins in Yeast ferments sugar. But what is this thing?

The protein itself? Surely not!

Then, along comes this guy:



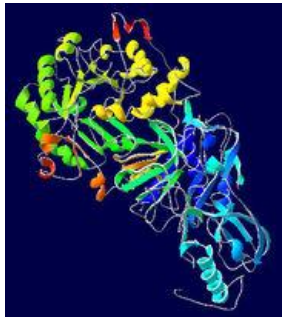
James B. Sumner
1887-1955

He starts trying to isolate an enzyme in it's pure form

In 1926 he gets crystals of Urease

He is then generally ignored for the next 10 years or so

In 1929, Northrop and Stanley do the same with ***Pepsin*** and now people start to believe (slowly)



1946

http://nobelprize.org/

John H.
Northrop

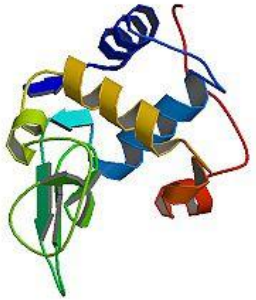
Wendell ***M.***
Stanley

Pioneers of Enzyme Function

Lord David Chilton Phillips (1924 – 1999)

Got X-ray crystal structure for Lysozyme in 1965

The beginning of ***Structural Biology***



We now know the structure of lysozyme down to 1.04 Å (1.04×10^{-10} m, C-H bond ~1.1 Å).

Leonor Michaelis
1875–1949

Maud Menten
1879–1960

Pioneered enzyme kinetics

"I think that enzymes are molecules that are complementary in structure to the activated complexes *of the reactions that they catalyse, that is, to the molecular configuration that is intermediate between the reacting substances and the products of reaction for these catalysed processes.* The attraction of the enzyme molecule for the activated complex would thus lead to a decrease in its energy, and hence to a decrease in the energy of activation *of the reaction, and to an increase in the rate of the reaction" - 1948*

Chemistry (1954)

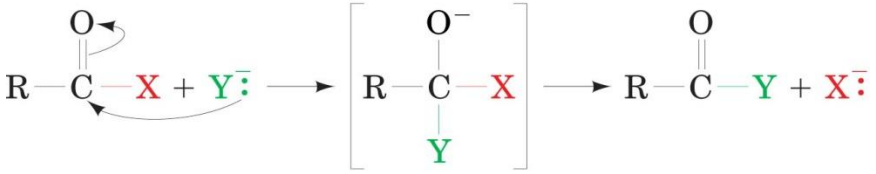
Peace (1962)

Metabolism Overview – Organic Chemistry

- All metabolic chemistry falls under one of the following 4 categories:

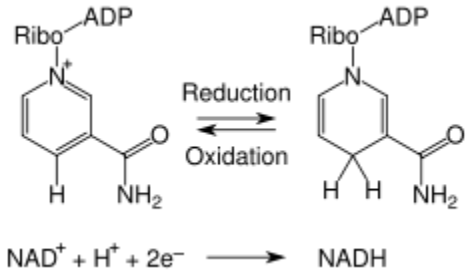
1. Group transfer
2. Oxidations and Reductions
3. Elimination / Isomerization
4. Carbon bond making/breaking

- Group transfer:



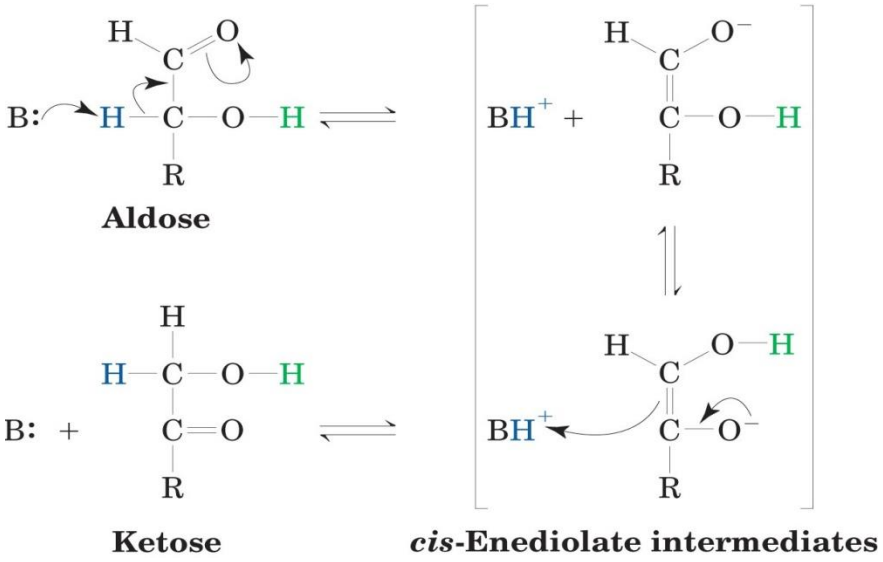
Tetrahedral intermediate

- Oxidation/reduction:



More Organic Chemistry

- Elimination / Isomerization:



- Carbon bond making/breaking: