An overview of biochemistry for bioCHEM480
These are some of the most important topics in covered in an introduction to macromolecular biochemistry in this course:

- Acid-Base chemistry, the concept of pK\textsubscript{A}, conjugate acid/base pairs, and the use of Henderson-Hasselbalch equation V\textsubscript{2} (i.e. Voet, Voet and Pratt Chapter2)
- Principles of bio-energetics; the laws of thermodynamics, equilibria, kinetics, Enthalpy & entropy V\textsubscript{1}, V\textsubscript{12}
- Non covalent interactions (NCIs) and specific intermolecular recognition (SIR) V\textsubscript{2}
- Functional groups in organic compounds & their major reactions including redox reactions
- Amino acids; classification by types of “R” groups V\textsubscript{4}
- The peptide bond and protein structures (primary, secondary and tertiary) V\textsubscript{4} & 5
- Collagen and elastin; structure/activity/biological function relationship of fibrous proteins V\textsubscript{6}
- Myoglobin & Hemoglobin; structure/activity/biological function relationship of globular proteins V\textsubscript{7}
- The structure-activity-biological function relationship of saccharides V\textsubscript{8}
- Plasma membranes; structure/activity/biological function relationship of lipids V\textsubscript{9}
- Lipid digestion and transport by lipoproteins and atherosclerosis V\textsubscript{20}
- Membrane transport V\textsubscript{10}
- Enzymes: activity, efficiency, specificity active/binding/catalytic sites, V\textsubscript{10}
- Enzyme kinetics; Michaelis-Menten, Lineweaver-Burk plots, and regulation V\textsubscript{12}
- The structure-activity-biological function relationship of nucleic acids V\textsubscript{3}
- DNA sequencing and DNA engineering V\textsubscript{3}

For future reference

The bioCHEM 481 course (‘Intermediary Metabolism’) will concentrate on biochemistry as it relates to:

- Biochemical signaling V\textsubscript{13}
- Overview of metabolism V\textsubscript{14}
- Chemical energy production and consumption; oxidative phosphorylation V\textsubscript{14} & 18
- Metabolism of carbohydrates: glycolysis, TCA cycle, gluconeogenesis, PPP, glycogenolysis and glyconeogenesis V\textsubscript{15}, 16 & 17
- Metabolism of triacylglycerols: degradation and synthesis of fatty acids V\textsubscript{20}
- Metabolism of amino acids. V\textsubscript{21}

The bioCHEM 482 course will concentrate on biochemistry as it relates to:

- The integration of metabolism by different organs and hormones to maintain a dynamic equilibrium in mammals.
- The molecular processes of nucleotide metabolism in eukaryotic cells, particularly, mammalian tissues.
- The molecular processes in photosynthesis in plant and bacterial cells.
- The relationship between biochemical events at the molecular level to physiological processes in whole animals.
- The correlations of abnormal biochemical processes with human diseases and syndromes.
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- The correlations of abnormal biochemical processes with human diseases and syndromes.
Why is life the way it is?
What is the meaning of life?
What is answer to the Ultimate Question of Life, The Universe, and Everything? [42?]
It starts here........

5 major tenets of biology/biochemistry

Cell theory: Hooke, van Leeuwenhoek, Schleiden and Schwann
Evolution: Natural selection: Darwin & Wallace
DNA and information flow: The Central Dogma: Watson and Crick & (now) Epigenetics
Energy: Transduction from light and chemicals to useful energy (ATP) Mitchell
Regulation...homeostasis and adapting to changes at the molecular/cellular levels.

Living organisms are remarkably similar at the molecular level** despite the observed biological diversity. In nature, there exists a biochemical unity of diverse living organisms in that there is a wide range of adaptations around a common chemical framework (Can you name some common compounds found in all living species?). This embodies just the use of a few elements i.e. mainly NCHOPS that exploits the ability of C (and N to a lesser extent) to form strong (single and double) covalent bonds to both to itself and these other elements, especially HNOS (with linear, cyclic and branched skeletons) together with a limited number of metal cations (Na, K, Ca, Mg, Mn, Fe, Co, Zn, etc.) to form neutral, cationic and anionic chemical species. The unique feature of all living cells is the way in which so many reactions that take place in the organelles of cells (and cells in tissues and tissues in organs and organs in organisms and organisms in ecosystems, etc) are organized to serve a single purpose, "life"!

**However, there some significant differences between 'biological domains', see table below i.e. (1) the ability of some archea to survive in zero oxygen and seemingly hostile conditions, i.e. >80°C, high pressures, high salt, etc), (2) the invention of photosynthesis by bacteria (and passed on to plants), (3) the possession of cytoskeletons by eukarya allowing for large and complex cell structures.(4) different redox chemistry, etc

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Organisms</th>
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<tbody>
<tr>
<td>photosynthesis</td>
<td>plants and cyanobacteria</td>
</tr>
<tr>
<td>nitrogen fixation</td>
<td>specialized soil bacteria</td>
</tr>
<tr>
<td>oxidation or reduction of inorganic minerals</td>
<td>archaeabacteria</td>
</tr>
<tr>
<td>acid- and gas-producing fermentations</td>
<td>anaerobic bacteria</td>
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The underlying commonality of biochemical processes are briefly reviewed in the following 12 concepts. Before you embark as a student in this biochemistry course you should read these concepts for understanding.

1. **Cells: their role and their contents.** The cell is the fundamental unit of life. Cells, whether they be unicellular or multi-cellular organisms, must operate as "open" thermodynamic systems by establishing a dynamic equilibrium with the local micro environment. Living organisms create and maintain a complex system using energy (solar or chemical) extracted from the environment and they have the ability to discharge wastes.
Thermodynamics applications to the cell includes: enthalpy (bond breaking and formation), entropy (order/disorder), free energy ($\Delta G=\Delta H-TS$), kinetics & catalysis ("enzymes") and energy ‘coupling’ (to ATP).

There is no such item as an ‘average cell’. What makes then different?

All cells are composed of a mixture of (a) small chemical species (organic and inorganic), (b) intermediate-sized organic compounds, (c) macro-molecules and (d) organelles in a clear hierarchy (see figure on following page).

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The molecular organisation of the cell involves the: genome, epigenome, transcriptome, proteome, & metabolome. Not all genes are expressed in the same cell at the same time! Consequently
there must be elaborate control of transcription by chemical signaling, receptors, feedback mechanisms via transcriptional factors etc. Further there is a need for post transcriptional and translational chemical “processing”

**The Hierarchy of Biological Structure**

![The Hierarchy of Biological Structure](image)

**Fuel Metabolism:**

A successful organism has to be able to synthesize compounds not supplied by the diet in order to survive. This includes compounds of high chemical potential energy (i.e. ATP) for both growth, development and for protection of its internal environment from variable external conditions (i.e. from the well-fed to starvation states, temperature, O\(_2\) availability, xenobiotics, etc).

Five processes are required: LADME *(for more see Introduction in Palmer’s book)*

1. **L** = Liberation: conversion of nutrients in the diet into *usable* compounds,
2. **A** = Absorption: mainly in the intestines where
digestive enzymes catalyse the conversion (via hydrolysis reactions) of proteins to amino acids, complex carbohydrates to (mainly) glucose, fats/oils to fatty acid carboxylates (RCO₂⁻) and glycerol as in the reverse of the arrows in the diagram above for proteins polysaccharides and triglycerides. In addition, the gut microbiota in humans appear to play a pivotal role in both health and disease. In a healthy state, the gut microbiota have myriad positive functions, including energy recovery from metabolism of nondigestible components of foods, protection of a host from pathogenic invasion, and modulation of the immune system. Further, lack of them is anecdotally associated with a number of diseases, syndromes and ‘functional aberrations’. The bacteria harbored within the human gastrointestinal tract (GIT) ("gut microbiome") outnumber the host’s cells by a factor of 10 and the genes encoded by the bacteria resident within the GIT outnumber their host’s genes by more than 100 times.

(3) **D=Distribution**: the initial products from digestion are transported away from the intestines by the blood and lymphatic fluids to different organs. Some of these compounds are water insoluble and require transport proteins.

(4) **M=Metabolism**: this includes (i) oxidation of energy-rich metabolites (see section 6 page 8) to transduce the chemical energy stored in the chemical bonds of these metabolites to chemical energy stored in ATP (ii) storage and subsequent mobilization of new energy-rich compounds, (iii) biosynthesis of crucial metabolites and non-fuel macromolecules (proteins, poly-nucleotides, some polysaccharides, etc)

(5) **E=Excretion**: elimination of waste metabolites and detoxification processes in waste disposal pathways mainly in the liver
2. Macromolecules. Macromolecules are ubiquitous in all living species and have complex but somewhat flexible structures. They store and express genetic information, provide for compartmentation, regulate many functions, and importantly, allow for biological specificity by specific inter/intra-molecular recognition (SIR). Macromolecules fold into complex 3-D structures (‘conformations’) in such a way as to enhance their stability by maximizing intra- (i.e. internally within the macromolecule) and inter- (between the macromolecule and the solvent-usually water except in membranes and micelles) molecular non-covalent interactions (‘NCI’). Macromolecules spontaneously fold to achieve the conformation of highest thermodynamic stability that is or is very close to the conformation of the highest biological activity. It should be noted that this folding is a dynamic process and these macro-molecules can take up more than one conformation, and there is a constant switching between the conformations (in equilibria) dominated by the drive to thermodynamic stability under possibly constantly changing micro-environments (i.e. temperature, pH).

The driving forces for the formation of these 3D structures is considered to be predominately entropically driven. Recall that for any spontaneous process ($\Delta G^0 = \Delta H^0 - T\Delta S^0$), $\Delta G^0$ must be <0.
Consider the folding of a protein from the random or unfolded conformation just formed on the ribosome to forming its native or folded conformation. The NCI NET enthalpy changes is ~0, but the spontaneity in vivo requires NET ΔS°>0.

Initially, water molecules have to form 'cages' that surround the nonpolar or hydrophobic ‘R’ groups of the amino acid residues in the random conformation. As the macromolecule folds these non-polar groups on the polypeptide chain form a non-polar core that stabilises the macromolecule by the 'expulsion or freeing up' (to bulk solution) of these water molecules. The effect of this is to cause extensive disorder of the water molecules and thus ΔS° is NET positive and thus drives the NET spontaneous folding (with ΔG°<0).

Some proteins (especially multi sub-unit and/or multi-domain proteins) are known to use other proteins (disulfide isomerases V4 and chaperonins V5) to catalyse these protein folding processes.

Many of these individual macro-molecules with specific biochemical roles then spontaneously self assemble into "supra-molecular assemblies" (such as chromosomes, ribosomes, multi-enzyme complexes, membranes, see hierarchy diagram above).

The chemical structure and the micro environment of a macromolecule determines its chemical (re)activity which in turn determines its biological function. This is known as the 'structure/activity/biological function' (SAF) relationship [St->Act->Biol.Funct.].

Thus any changes in structure (chemical or conformational: temporary or permanent) will cause changes in activity and function [ΔSt->ΔAct->ΔBF]. An example is a protein becoming 'denatured' by changes in pH; ΔpH->Δ[Conjugate Base or CA]/[Conjugate acid or CA] for every ionisable group - ΔNCI->ΔStructure/conformation->ΔActivity->ΔBiolFunct).

Sickle cell anaemia represents another example: (V7) This disease is caused by a gene mutation that leads to a change in amino acid residue on the surface of the β subunit from HbA (the β6 is a Glu) to HbS (β6 is a Val). Thus, comparing HbA and HbS, there will be an alteration of the type of NCIs that in which these ‘R’ groups will be involved. This HbA Glu will be solvated by water whereas in HbS, the Val non-polar hydrophobic ‘R’ group. To ‘avoid’ this exposure of the isopropyl group in Val to water, HbS under certain conditions, changes its structure and aggregates into insoluble fibrils. Thus a change in structure causes changes in NCIs that causes changes in structures that in turn causes a change in biological function (i.e. decreased ability to transport of O2).

Other examples include (1) cystic fibrosis (CF) usually caused by a 3 base/1 amino acid residue deletion in the CFTR protein that results in misfolding than leads to a change in membrane permeability, (V9) and (2) phenylketonuria (PKU) caused by mutations in the PAH gene and thus diminished enzyme activity cause a buildup of Phe (and some of its catabolites) that has a deleterious physiological effect. (V21)

Most macromolecules are chemically altered or processed from their initial formation to the mature, active conformation. Examples include (i) modification of amino acid residues in collagen V5, (ii) addition of the heme unit to hemoglobin, myoglobin, and cytochromes, (iii) covalent modification by phosphorylation in regulatory enzymes, (iv) formation of glycoproteins, proteoglycans and glycolipids V8 (v) conversion of the primary transcript (hnRNA) to the mature mRNA in eukaryotes and, (vi) the methylation and acetylation of the bases of DNA and the histones in the chromosomes (in ‘epigenetics’). Most processing requires specific enzymes and represents a form of regulation in vivo.

3. Biochemical Reactions. The biochemical reactions that take place within the cell are a subset of ordinary organic reactions. The same rules of electron flow (related to (a) relative bond strengths (b)
bond breaking & formation, (c) orbital interactions of nucleophilic and electrophilic atoms/sites and thermodynamic stability of reaction intermediates apply in vivo as in vitro as do the laws of thermodynamics! Biochemistry, as most generalised texts currently present it, is a continuation of organic chemistry but in a special medium (water, pH7.4, ionic strength ~0.2M, 37°C, etc). The typical undergraduate biochemistry course is in essence an advanced organic chemistry course that features the molecules and chemical processes of 'life' (see earlier). As you study it, you will draw heavily on what you learned in organic chemistry, as well as general chemistry i.e. bioenergetics). Examination of a pathway, i.e. glycolysis (V15), TCA cycle (V17), and FA catabolism (V20) of the proteins, fats/oils and carbohydrates, etc will reveal types of reactions covered on organic chemistry; i.e. dehydration of alcohols, formation and hydrolysis of esters, amide and acetals, aldol/Claisen/mixed aldol-Claisen condensations, oxidation of alcohols and aldehydes, etc. One major omission in the undergraduate curriculum is the ubiquitous (in vivo) nucleophilic substitution at P=O that is usually not covered but is analogous to the same type of reaction at C=O (via a pentahedral rather than tetrahedral intermediate) requiring incoming nucleophiles and leaving groups usually phosphates or thioethers).

4. Metabolic Pathways. Biochemical reactions are organised in specific 'metabolic' pathways (glycolysis, gluconeogenesis, FA catabolism and synthesis, PPP (V15) amino acid and nucleoside catabolism and synthesis V23, etc. Many intermediary metabolites ['IM'] (i.e. glucose-6’P, pyruvate, acetyl-CoA, succinate, asp(D), glu(E) etc.) serve more than one function, i.e. catabolised for energy (leading to ATP formation) or used as 'building' blocks for the synthesis of larger compounds (requiring ATP). For more click on these links Overview of Catabolism and ATP/NADP roles.

In order to achieve the optimal use of the ATP synthetised by an organism, it is crucial that the flux of chemicals through these pathways be regulated to prevent 'futile cycling'. Such regulation is achieved by control of the activities of specific enzymes by allosteric effectors, covalent modification, hormones, etc. (See #9 below for more.) The diagram below illustrates both some of the pathways and, importantly, the essential inter-connectivity of these pathways.

Adapted from Dr. Pedro Silva, www2.ufp.pt/~pedros/bq/integration.htm

It is crucial to the viability of a cell (and thus organisml) that these pathways are regulated
appropriately. This is accomplished by (1) allosteric interactions (2) covalent modification of enzymes (3) adjustment of local enzyme levels (4) compartmentation (see below # 8) and (5) metabolic specialization of organs.

A majority of the compounds in living organisms contain only C, H and O. The next most common combination is CHO and N (amino acids, proteins, nucleotides, etc). On a very basic level, ‘CHO’ ends up as CO₂ and water but with nitrogen containing compounds, organisms require specialised pathways to eliminate excess nitrogenous compounds. In humans, this is accomplished mainly by the formation and excretion of the very water-soluble urea in the urine. This is synthesised in the liver and elimination via the kidneys. Any ammonia transiently formed by the deamination of amino acids etc is transported from most tissues to the liver where the N is incorporated into urea by the urea cycle requiring ATP. The urea and TCA cycles are chemically interconnected.

Transport of water insoluble IMs: There are a limited number of compounds of low solubilities in water (i.e. O₂, cholesterol, TAG, FFA) so these need specific transport pathways to ensure the appropriate concentrations of such compounds at their specific sites of action.

5. Enzymes. Most, but not all, reactions in vivo would effectively NOT take place (especially under the special conditions of most cells) without the presence of specific enzymes. All (almost!) biochemical reactions take place in active sites of enzymes: substrates bind customised binding sites and the chemistry (bond breaking and formation) of the reactions are controlled by the catalytic site of the enzyme. There is electronic (by NCIs) and steric (by space requirements) complementarity between the substrates and the binding sites. The substrates "dock" onto the binding sites in specific orientations (this controls the regiospecificity of reactions) in such a way that the flow of electrons (see #3 above) allowed in the "catalytic site" is in only one specific direction (this controls the stereospecificity of reactions).

The presence of enzymes is the key to what reactions actually take place (and at what rate) at a specific biological site given that there usually many hundreds of compounds available at any such site. Specific inter- and intra-molecular recognition (SIR) is one of the characteristics of biochemistry and is especially important in enzyme specificity. The rates of biochemical reactions (and thus the rate of accumulation of products) are controlled by the concentration of enzymes in their ‘active’ conformation. [Enz]active. [Enzyme] is controlled (at a ‘coarse’ level) by both the rate of formation of the hnRNA from the gene and rate of processing of the hnRNA to mRNA (..and this latter process is highly regulated by small RNA molecules). Other types of enzyme activity ‘fine’ regulation are allosterism and hormone-controlled covalent modification by phosphorylation (requiring ‘kinases’) and dephosphorylation (requiring phosphatases). See Vp617 for an example These enzymes can be regulated in well organised in ‘enzyme cascades’ (See Vp424 & 535 for an example)

Flux in biochemical pathways is regulated by changes in the activities of specific enzymes. Enzymatic activity is regulated by multiple mechanism including (1) binding via NCIs of specific intermediary metabolites (allosteric regulators), e.g. ATP, ADP, NAD⁺, NADH, NADP⁺, NADPH etc. using negative feedback and forward activation, (2) reversible covalent modification often by phosphorylation/dephosphorylation of AA residues such as Tyr(Y) and Ser(S) on the protein in reactions that require specific enzymes and (3) by hormonal directed activation/deactivation of proteins). See Vp617 for an example These enzymes can be regulated in well organised in ‘enzyme cascades’ (See Vp424 & 535 for an example)

Click these links for examples of regulation in these specific pathways: TCA &
Glycolysis. Many enzymes, especially transferases (V11), require non-protein ‘co-factors’ for full biological activity. These co-factors can be metal ions, coenzymes (derived from water soluble vitamins (V14) heme, etc. Some are bound to the enzyme by non-covalent interactions (NCIs) and other by covalent bonds.

6. Redox Reactions: Deriving Energy. The basis of virtually all energy transduction processes in living cells is through redox reactions (i.e. electron flow) Oxidation reactions (involving release of electrons) are nearly always exothermic/exogonic whereas reduction reactions (involving acceptance of electrons) are nearly always endothermic/endogonic. Thus food (carbohydrates, fats/oils and proteins) is digested in the intestines by hydrolysis reactions to products (glucose, fatty acids, glycerol and amino acids) that can cross the epithelial cells into the bloodstream and are subsequently (in catabolic processes) oxidised by converting high energy C-H bonds into C=O in a two part process involving (1) hydride ion transfer from 'intermediary metabolites' to NAD⁺ and FAD (nature's two oxidising agents) and (2) recycling/oxidizing the resultant NADH & FADH₂ back to NAD⁺ & FAD by the reducing agent oxygen (usually) with the concomitant formation of ATP from ADP & Pi in the mitochondria. V14

Biosynthesis is NET reduction and so requires a reducing agent (NADPH) and an energy source (ATP)
7. Synthetic Reactions: Using Energy. Many biochemical synthetic reactions require energy: this is usually carried out by chemically activating (1) one substrate by reaction with ATP (or its equivalent, UTP, GTP, CTP, etc) to form phosphate esters or mixed carboxylic/phosphoric anhydrides or (2) activating an enzyme by phosphorylating specific functional groups (i.e. OH in amino acid residues). Thus is the exogonicity of one reaction (ATP to ADP or AMP) is used to 'drive' the endogonicity of another reaction so that the NET $\Delta G^o$ must be $<0$
Examples: ATP Coupled reactions Activation of amino acid for transfer to tRNA

8. Compartmentalization. Biochemical reactions are localised in time and space in a cell and indeed in multicellular organisms (you!), different organs (see below just related to digestion). Compartmentation is a key to a cell's and organism's organisation. This separation is maintained by water insoluble lipid membranes. However, these organisational processes decrease entropy and thus require energy for the synthesis and subsequent assembly of the membranes but the NET result is $\Delta G^o$
9. Signal transduction. Communication between different tissues is required in multi-cell organisms. This requires hormones (that can be proteins, peptides, steroids and amines) to be released by one tissue to cause one or more biochemical changes in another tissue. Membrane-bound receptors initially bind (by specific NCIs) these chemical messengers (V13) and change the 'biochemistry' (the pathways) inside the cell.

10. Genome to Proteome and back!

Conventional version

![The Central Dogma](https://example.com/image.png)

Current version

![Current Central Dogma](https://example.com/image.png)

Genetic information is stored as DNA (using mainly only four different bases (A,G,C & T) and is used to direct the synthesis of proteins via RNA intermediates (using mainly four different bases (A,G,C & U) in virtually all organisms (except retroviruses). See Central Dogmas above The second diagram reflects the current ideas deduced from recent epigenetic studies that some small RNAs and protein histones are involved in the control of gene expression. This changes everything! Clearly a real "paradigm shift"

Each genus/species is defined by a distinct set of macromolecules coded from the genome. The last part of this course there will be coverage of proteins and nucleic acids. It is assumed that you are familiar with the fundamental building blocks of proteins, the amino acids, and of DNA & RNA, the nucleotide bases (see below) along with a general understanding of the structure of DNA and RNA, and how they are produced and, in the case of DNA, replicated, and of the genetic code.
The genetic code refers to the triplet sequence of bases in RNA that recognize the specific tRNA carrying amino acids to be incorporated into protein. Each triplet of ribonucleotides is called a codon and specifies a tRNA corresponding to one of the 20 amino acids, or it encodes a stop signal. A three-base code produces 64 possible triplet codons ($4^3$ or $4 \times 4 \times 4 = 64$), and each is used for an amino acid or a stop codon, so the genetic code is degenerate (that is, some amino acids are encoded by more than one codon). The codons are translated sequentially from a start site on the mRNA, an initiation codon, which is almost always AUG, which encodes methionine. The stop codons are UGA, UAA, and UAG. The genetic code is nearly universal, mitochondria excepted, but different organisms do use particular codons preferentially to insert the same amino acid.

The amino acids

By coverage of V4, you will need to be familiar with the structures (and roles in proteins of AA residues) of all the amino acids and their abbreviations (both three letter and one letter). The most important aspect is knowing the functional groups of each AA and how the AA are classified into useful groups NEUTRAL (polar/ aliphatic nonpolar/aromatic non-polar), IONIC (charged +/-), and whether the FGs are hydrophobic or hydrophilic or both!)

Manipulation of the Henderson-Hasselbalch equation is a must for this course!
11. **Biochemical Interconnectedness.** Organelles, cells and organisms are chemically dependent on each other (‘synergy’). Ecology for the day! To survive you have to be a hunter-gatherer in the wilds, your garden or at the supermarket for nutrients. All terrestrial species rely on the physical and chemical decomposition in soil of the wastes/dead of some organisms so that the decay products are the fuel for others ([N cycle image](#)). Nature is the ultimate recycler!

Many environmental problems have been caused by the induction and (over-)use of non-biodegradable compounds such as biocides including DDT- e.g. Rachael Carlson's *Silent Spring*, CFCs (stratospheric ozone thinning), PCBs, synthetic polymers -plastics, fibers, foams, paints, etc) in the last 150 years.

12. **Evolutionary Interconnectedness.** All successful organisms must be capable of self-assembly, self-replication, catalysis, and allow for some mutations. This is the basis of the evolutionary development of life. Biochemical systems have been evolving at least ~3.8 billion years and all living systems are related through a common evolutionary pathway. Living organisms are remarkably similar at the molecular level despite the observed biological diversity. Thus, in nature, there exists a biochemical unity of diverse living organisms in that there is a wide range of adaptations around a common chemical framework.