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REVIEW ARTICLE

THE EMERGENCE OF THE CLOSED 9-STEPPED CYCLE OF PROTON CONDUCTANCE THROUGH ELECTROPHILE - NUCLEOPHILE INTERACTIONS DURING BIOLOGICAL EVOLUTION

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ABSTRACT

The Ambaga Closed 9-Stepped Cycle of Proton Conductance is one of the most fundamental systems that emerged during biological evolution, and its formation was driven by the force of electrophile - nucleophile interactions. This is supported by the following scientific foundations: Origin of Life and the Role of Electrophile - Nucleophile Forces After the Big Bang, protons (H^+) and electrons (e^-) became the essential energy carriers of the universe. These charged particles established electrophilic (electron-accepting) and nucleophilic (electron-donating) forces as the fundamental chemical drivers in biological environments. 2. Release of Hydrogen Atoms from Food Molecules Initiates Proton Flow. During the first step of catabolism, hydrogen atoms are cleaved from food molecules (glucose, lipids, amino acids), generating electrons (e^-) and protons (H^+). This process is governed by electrophile–nucleophile reactions, where electron-accepting cofactors (e.g., NAD^+, FAD) act as electrophiles, and enzyme functional groups act as nucleophiles. 3. Each Step in the Proton Conductance Cycle Involves Electrophile - Nucleophile Interactions

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INTRODUCTION

By us discovered the following stages in the closed cycle of proton conductance: First stage of proton conductance: oxygen channeling to the mitochondria of 87 trillion cells; oxygen channeling: oxygen has been assumed to diffuse across cell bodies; very low oxygen solubility in the cytosol, reported High-solubility 'channels' likely formed by the endoplasmic reticulum by hemoglobin-bearing cytochrome P450 molecules; accelerated oxygen diffusion via lipid droplets; lateral diffusion within mitochondrial membranes; mitochondria; release of hydrogen atoms, protons, and electrons from food molecules; Krebs cycle under the influence of the ninth stage as release of oxygen from hemoglobin. The second stage of proton conductance is carbon dioxide, generated by the Krebs cycle in the mitochondria of 87 trillion cells. Third stage: the processes conducted in connection with the formation of NADH, FADH, Coenzyme Q, and Cytochrome C oxidase

Fourth stage: the processes conducted with the formation of a proton gradient from protons and the connection of oxygen with electrons.

The fifth stage: the processes conducted with the formation of ATP, heat energy, and metabolic water.

The sixth stage: formed in the mitochondria diffuses into plasma and into red blood cells. The capillary blood of respiratory membranes reacts with metabolic water to form H_2CO_3 and HCO_3. From the mitochondria, carbon dioxide diffuses into the plasma and into red blood cells.

Seventh stage: In the red blood cells of the capillary blood of the respiratory membranes, protons dissociate from hemoglobin and bind with HCO_3 (entered by chloride shift) - uptake of oxygen by hemoglobin. In the red blood cells of capillary blood, a CL shift occurred between mitochondria, plasma, and hemoglobin.

Eigth stage of proton conductance: proton release from R-state hemoglobin enhances CO_2 release in the respiratory membranes of the lungs; the dramatic increase in the partial pressure of oxygen drives the binding of oxygen to deoxyhemoglobin; O_2 binding triggers the transition of T-state hemoglobin to R-state hemoglobin. Oxygen diffuses into the plasma and into red blood cells from the alveolus. Oxygen binds to hemoglobin; in the chloride shift, as HCO_3 diffuses into red blood cells, bicarbonate ions and protons combine to replace H_2CO_3, carbon dioxide is released from hemoglobin, and hydrogen ions are released from hemoglobin.

Ningh stage of proton conductance: binding of protons to T-state hemoglobin increases CO_2 uptake from respiring tissues. As R-state hemoglobin gives up its bound oxygen to respiring tissues and subsequently transitions to the T-state, it drives the release of oxygen from hemoglobin to the mitochondria of 87

trillion cells. Carbon dioxide and hydrogen ions combine with hemoglobin, which has released oxygen, to promote the release of oxygen from hemoglobin. Oxygen is released from hemoglobin, which diffuses out of red blood cells and plasma into tissues (the mitochondria).

RESULTS

The Closed 9-Stepped Cycle of Proton Conductance is one of the most fundamental systems that emerged during biological evolution, and its formation was driven by the force of electrophile - nucleophile interactions. This is supported by the following scientific foundations:

Origin of Life and the Role of Electrophile - Nucleophile Forces:

After the Big Bang, protons (H^+) and electrons (e^-) became the essential energy carriers of the universe. These charged particles established electrophilic (electron-accepting) and nucleophilic (electron-donating) forces as the fundamental chemical drivers in biological environments.

Release of Hydrogen Atoms from Food Molecules Initiates Proton Flow

During the first step of catabolism, hydrogen atoms are cleaved from food molecules (glucose, lipids, amino acids), generating electrons (e^-) and protons (H^+). This process is governed by electrophile - nucleophile reactions, where electron-accepting cofactors (e.g., NAD^+, FAD) act as electrophiles, and enzyme functional groups act as nucleophiles.

Each Step in the Proton Conductance Cycle Involves Electrophile–Nucleophile Interactions

Each of the nine stages of the Ambaga Closed 9-Stepped Cycle of Proton Conductance, identifying where electrophiles and nucleophiles play a role in redox and bioenergetic transformations.

Stage 1: First stage of proton conductance: oxygen channeling to the mitochondria of 87 trillion cells; oxygen channeling: oxygen has been assumed to diffuse across cell bodies; very low oxygen solubility in the cytosol, reported High-solubility 'channels' likely formed by the endoplasmic reticulum by hemoglobin-bearing cytochrome P450 molecules; accelerated oxygen diffusion via lipid droplets; lateral diffusion within mitochondrial membranes; mitochondria; release of hydrogen atoms, protons, and electrons from food molecules; Krebs cycle under the influence of the ninth stage as release of oxygen from hemoglobin. Electrophiles such as NAD and FAD accept hydrogen atoms containing protons and electrons from nucleophilic sites on food molecules.

Stage 2: CO_2 Formation (Krebs Cycle Integration).

Main event: Oxidative decarboxylation, release of CO_2.

Electrophile: NAD^+ or FAD, accepting electrons from intermediates.

Nucleophile: Substrate-derived electrons from α-ketoglutarate, etc.

Mechanism: CO_2 is released as a product of redox-driven nucleophilic attacks.

Stage 3: Membrane Redox Potential Establishment

Main event: Electron flow builds membrane potential.

Electrophile: Quinone (Q) accepts electrons (e.g., CoQ in mitochondria).

Nucleophile: Electrons from NADH/$FADH_2$.

Mechanism: Redox reactions involve nucleophilic transfer of electrons across membrane complexes.

Stage 4: ATP Synthesis Begins

Main event: Protons flow through ATP synthase.

Electrophile: ADP and Pi, electrophilic phosphate groups accept energy.

Nucleophile: Proton-coupled electrons, enabling nucleophilic attack on Pi to form ATP.

Mechanism: ATP formed through nucleophilic condensation.
Stage 5: Metabolic Water Formation

Main event: Reduction of O_2 to water

Electrophile: Oxygen (O_2) - strong electrophile.

Nucleophile: Electrons from cytochrome c, protons combine with oxygen.

Mechanism: Final electron acceptor; classic electrophilic substitution reaction forming H_2O.

6th Stage: Formation of Carbonic Acid and Proton–Bicarbonate Equilibrium

Reaction Overview (in blood serum):

$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

Catalyzed by carbonic anhydrase (carboanhydrase). Electrophile and Nucleophile Roles in the 6th Stage

CO_2 (Carbon Dioxide) - acts as an electrophile:

CO_2 is electron-deficient at the carbon atom, seeking electron pairs. It reacts with H_2O, which donates a lone pair (nucleophilic attack on CO_2) forming carbonic acid. H_2O (Water) - acts as a nucleophile:

Its oxygen donates a lone electron pair to carbon in CO_2, forming H_2CO_3 (carbonic acid). Carbonic Acid (H_2CO_3) - acts as a proton donor (acid):

Undergoes dissociation:

$H_2CO_3 \rightleftharpoons H^+$ (proton) + HCO_3^- (bicarbonate)

HCO_3^- (Bicarbonate) - acts as a nucleophile:

It can react further (later in buffering systems and transport), and prepares for entry into erythrocytes.

Proton (H^+) - is an electrophile:

Very reactive, participates in pH regulation, and later facilitates O_2 release in the 9th stage.

Main event: O_2 dissociates from Hb as protons and CO_2 bind.

Electrophile: Fe^{3+}-bound O_2 (weakened by Bohr effect).

Nucleophile: H^+ and CO_2, promote release via nucleophilic substitution.

Mechanism: Nucleophilic substitution pushes out O_2 in tissue

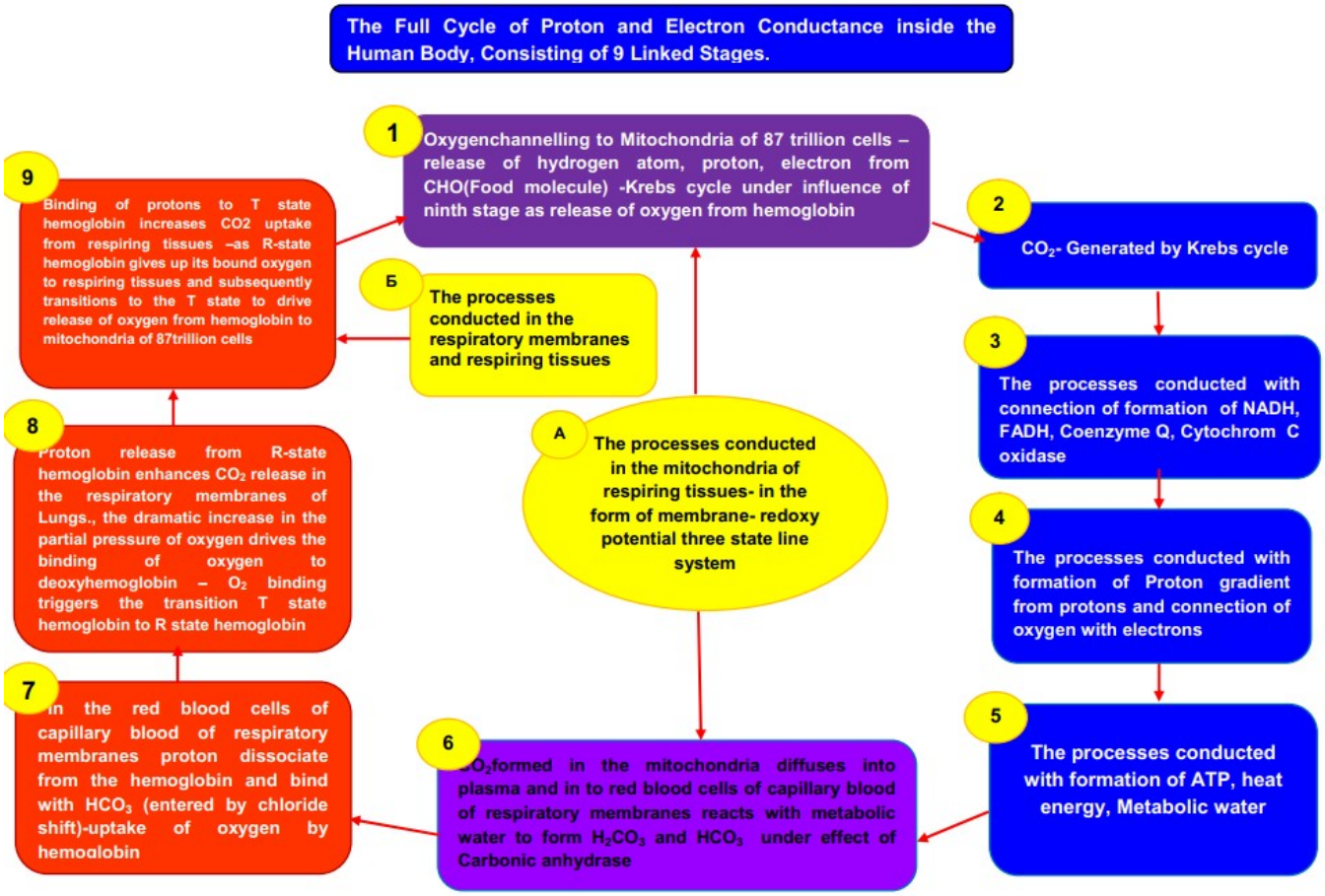

Figure 1. The Closed 9-Stepped Cycle of Proton Conductance

Stage 7: Membrane Transfer & Preparation for the Hamburger Shift

The bicarbonate ion (HCO_3^-) is transported into the erythrocyte membrane via anion exchange protein (Band 3). This is the preparation stage for the Hamburger shift, which maintains charge neutrality and prepares the system for oxygen release at tissues (Stage 8: Oxygen Uptake in Lungs, 9th stage).

Stage 8: Oxygen Uptake in Lungs

Main event: Hemoglobin binds O_2 in pulmonary capillaries.

Electrophile: Oxygen (O_2) binds to Fe^{2+} in Hb.

Nucleophile: Fe^{2+} in hemoglobin acts as electron-rich center.

Mechanism: Electrophilic substitution, oxygen binds to Fe^{2+}.

Stage 9: Oxygen Release in Tissues.

CONCLUSION

The Ambaga Closed 9-Stepped Cycle of Proton Conductance is one of the most fundamental systems that emerged during biological evolution, and its formation was driven by the force of electrophile - nucleophile interactions. This is supported by the following scientific foundations:

Origin of Life and the Role of Electrophile - Nucleophile Forces. After the Big Bang, protons (H^+) and electrons (e^-) became the essential energy carriers of the universe. These charged particles established electrophilic (electron-accepting) and nucleophilic (electron-donating) forces as the fundamental chemical drivers in biological environments.

Release of Hydrogen Atoms from Food Molecules Initiates Proton Flow

During the first step of catabolism, hydrogen atoms are cleaved from food molecules (glucose, lipids, amino acids), generating electrons (e^-) and protons (H^+). This process is governed by

electrophile–nucleophile reactions, where electron-accepting cofactors (e.g., NAD^+, FAD) act as electrophiles, and enzyme functional groups act as nucleophiles.

Each Step in the Proton Conductance Cycle Involves Electrophile–Nucleophile Interactions

According to the full nine-step cycle of electron and proton conductance inside the human body, as proposed by us:

First stage of proton conductance: oxygen channeling to mitochondria of 87 trillion cells; oxygen channeling: oxygen has been assumed to diffuse across cell bodies; very low oxygen solubility in the cytosol, reported High-solubility 'channels' likely formed by the endoplasmic reticulum by haem-bearing cytochrome P450 molecules; accelerated oxygen diffusion via lipid droplets; lateral diffusion within mitochondrial membranes; mitochondria; release of hydrogen atoms, protons, and electrons from food molecules; Krebs cycle under the influence of the ninth stage as release of oxygen from hemoglobin. The second stage of proton conductance is carbon dioxide, generated by the Krebs cycle in the mitochondria of 87 trillion cells.

Third stage: the processes conducted with connection to the formation of NADH, FADH, Coenzyme Q, and Cytochrome C oxidase.

Fourth stage: the processes conducted with the formation of a proton gradient from protons and the connection of oxygen with electrons.

Fifth stage: the processes conducted with the formation of ATP, heat energy, and metabolic water. In the sixth stage, PO_2 formed in the mitochondria diffuses into plasma and into red blood cells. The capillary blood of respiratory membranes reacts with metabolic water to form H_2CO_3 and HCO_3. From the mitochondria, carbon dioxide diffuses into the plasma and into red blood cells.

Seventh stage: In the red blood cells of the capillary blood of the respiratory membranes, protons dissociate from hemoglobin and bind with HCO_3 (entered by chloride shift) - uptake of oxygen by hemoglobin.

In the red blood cells of capillary blood, CL shift occurred between mitochondria, plasma, and hemoglobin. Eigth stage of proton conductance: proton release from R-state hemoglobin enhances CO_2 release in the respiratory membranes of the lungs; the dramatic increase in the partial pressure of oxygen drives the binding of oxygen to deoxyhemoglobin; O_2 binding triggers the transition of T-state hemoglobin to R-state hemoglobin. Oxygen diffuses into the plasma and into red blood cells from the alveolus. Oxygen binds to hemoglobin; in the chloride shift, as HCO_3 diffuses into red blood cells, bicarbonate ions and protons combine to replace H_2CO_3, carbon dioxide is released from hemoglobin, and hydrogen ions are released from hemoglobin.

Ningh stage of proton conductance: binding of protons to T-state hemoglobin increases CO_2 uptake from respiring tissues. As R-state hemoglobin gives up its bound oxygen to respiring tissues and subsequently transitions to the T-state, it s to drive release of oxygen from hemoglobin to the mitochondria of 87 trillion cells. Carbon dioxide and hydrogen ions combine with hemoglobin, which has released oxygen, to promote the release of oxygen from hemoglobin. Oxygen is released from hemoglobin, which diffuses out of red blood cells and plasma into tissues (the mitochondria). In such way all processes including from Sixth stage – to Ningh stage of proton conductance may be describe as carbon dioxide diffuses in to the plasma and red blood cells (in the tissue capillaries), carbon dioxide is released from red blood cells, proton is released from red blood cells (in the pulmonary capillaries), oxygen diffuses in to plasma from alveolus, oxygen binds to hemoglobin, in the chloride shift as HCO_3 diffuses in to red blood cells, proton and carbon dioxide are combined with hemoglobin, that has released oxygen, promotes the release of oxygen from hemoglobin – oxygen diffuses out of red blood cells and plasma in to tissues – mitochondria of 87 trillion cells through oxygen channeling lipid based pathways.

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