Chemical synthesis and the combination with oxygen of heme

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Abstract. Heme is an essential compound in the human body. This work includes two main research summaries of heme and the chemical nature of this organic compound. The first part of this work includes specific processes, enzymes that be used, and situations where the synthesis of heme takes place. The next part is about how heme binds with oxygen and carries these molecules in body tissues and the effects of pH and temperature in combination with oxygen. The last part introduces a heme-dependent enzyme called catalase and how heme functions in this enzyme. Overall, this work contains most facts and specific illustrations of heme synthesis and its primary function. The meaning of this essay is to illustrate the process when heme binding with oxygen in the aspect of chemistry and explain other facts and functions of heme in the chemistry aspect.

Keywords: Heme, Synthesis of heme, heme binds with oxygen

1. Introduction

In this work, I explored an organic compound called heme in the human body, which includes the synthesis process, the combination with gases of heme. Heme is an essential organic compound in the human body with a particular structure with several functions, like transporting free electrons in organisms and binding with oxygen, then facilitating oxygen molecules throughout our bodies. The synthesis of this comparatively large molecule is quite complicated and the process of binding with oxygen is also complex. This process includes several steps and takes part in two organelles called cytosol and mitochondria with different enzymes to catalyse. The respiratory process also requires heme since heme can bind with four oxygen in haemoglobin by changing the shape of this protein and the orbitals in heme itself.

2. Chemical synthesis of heme

From Den, B.[1], The synthesis of heme takes place in both mitochondria and cytosol, which means the compounds in this process will be transported while these reactions occur. The first step in the formation of the first enzyme that is used in this synthesis, which is called δ-amino Levulinic acid(ALA). Glycine and Succinyl~coA are used in this step by a condensation reaction to form ALA in mitochondria.

ALA plays an important role for a compound called porphobilinogen, which is the original state of a quarter of heme. After ALA enters into cytosol, this reaction happens by dehydrating two moles of ALA to gain prophobilinogen.

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The third step demonstrates the condensation of four porphobilinogen. Four porphcilinogen will be catalyzed and converted into uroporphyrinogen-III in the cytosol.

The next step is the last step of gaining the iron ion from ferrochelation. "Then the side chains of uroporphyrinogen III are modified, catalyzed by uroporphyrinogen decarboxylase to produce coproporphyrinogen III." [2]. Coproporphyrinogen-III is formed by the conversion of the chains in unoporphyrinogen-III. After this process, coproporphyrinogen-III will be facilitated into mitochondria to finish the last step.

Coproporphyrinogen-III is oxidized to form protoporthyrinogen-IX and then this product will be oxidized again to produce protoporphyrin-IX. This terminal product during these condensation and oxidation reactions will ultimately gather a Fe+3 ion from ferrochelation, which means it has the capability to bind with oxygen now.

Figure 1 shows the overall synthesis of heme in mitochondria and cytosol and the structures of each compound that be used in the whole process and Figure 2 demonstrates the structures of each compound that is involved in the process of synthesis.

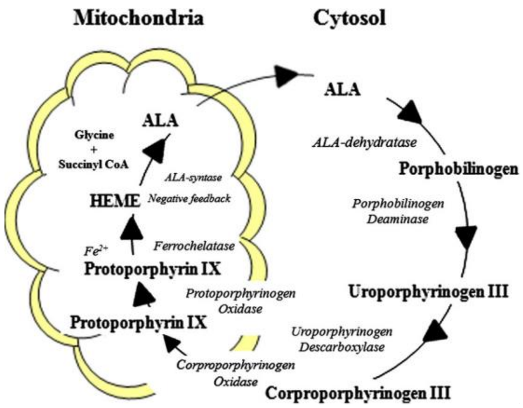

Figure 1. Dermatologica Sinica; Elsevier BV. Source: Zhang, L., Fang, Y., & Fang, J. (2011, March 1). *Heme synthesis pathway. ALA = 5-aminolevulinic acid.*[Picture]. https://doi.org/10.1016/j.dsi.2011.02.002

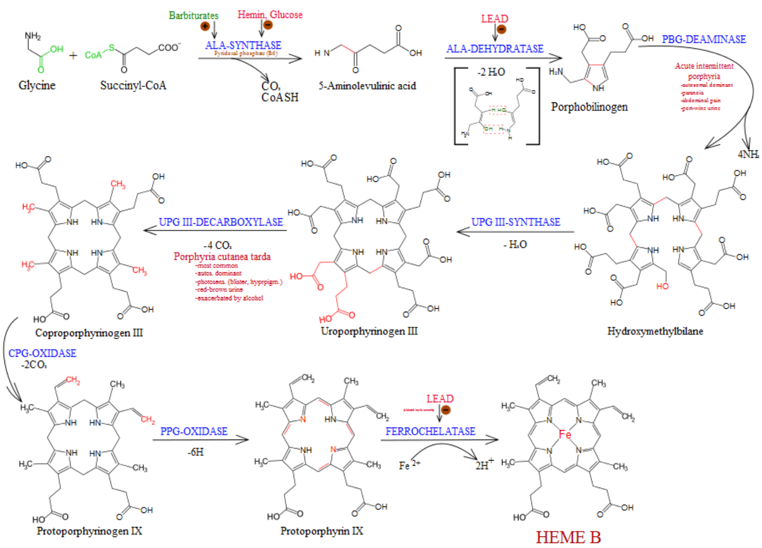

Figure 2. [Structures of compounds that be used in the process of synthesis] Biochemistry Den. Source: Den, B. (2023, January 25). https://biochemden.com/heme-synthesis/

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3. The process by which heme binds with oxygen and other gases

The combination with oxygen is another main focus in the study of heme. "A heme is made from 4 *pyrroles*, which are small pentagon-shaped molecules made from 4 carbons and 1 nitrogen. Four pyrroles together form a *tetrapyrrole*." [3]. Figure 3 below demonstrates a molecule of hemoglobin with four protein chains and the brief structure of heme.

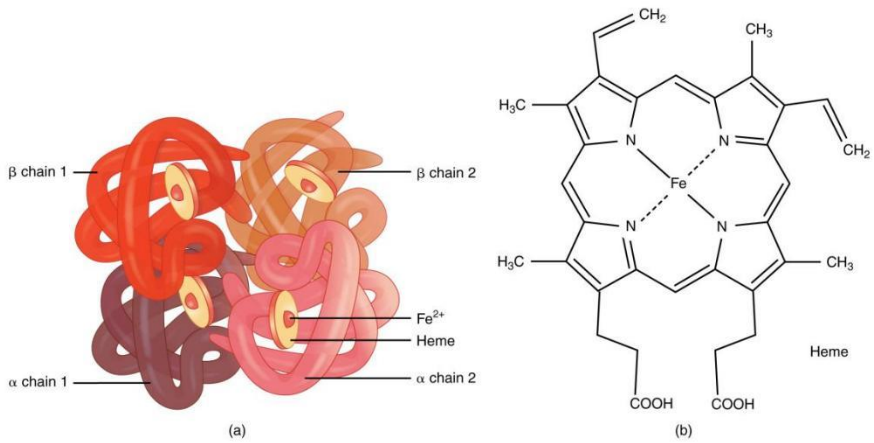

Figure 3. [Picture of (a) a molecule of hemoglobin with four protein chains and (b) the brief structure of heme](n.d.) Anatomy and Physiology. Source: https://philschatz.com/anatomy-book/contents/m46707.html

With the consideration of conjugation effect, due to the impact of π bond, each nitrogen atom should give a lone pair of electrons to enable the formation of a larger π bond. This means that the four nitrogen atoms should change their types of hybridization to be sp2 hybridized rather than sp3 hybridized apart from the iron ion in the middle. When the four nitrogen atoms use their lone pairs of electrons to coordinate with the iron ion, a fairly stable and electrically neutral chelate will be formed, which is also called a coordinate molecule.

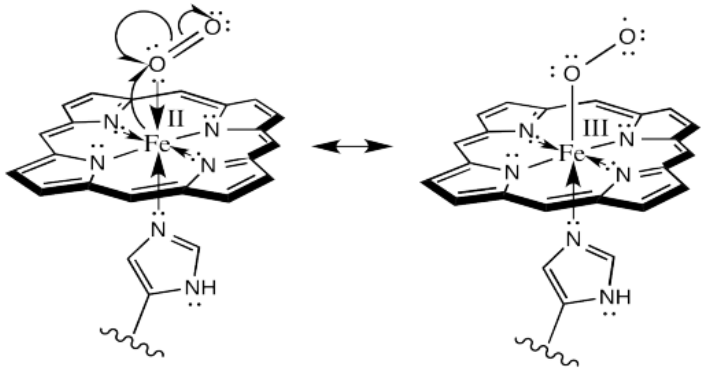

Figure 4. [Process by which heme bind with oxygen] Chemistry LibreTexts. Source: Schaller C. (2022, October 4). https://chem.libretexts.org/Bookshelves/General_Chemistry/Book%3A_Structure_and_Reactivity_in_Organic_Biological_and_Inorganic_Chemistry_(Schaller)/V%3A__Reactivity_in_Organic_Biological_and_Inorganic_Chemistry_3/04%3A_Oxygen_Binding_and_Reduction/4.02%3A_Oxygen_Binding.

According from Figure 4, one lone pair of oxygen can be attracted by the iron ion in the heme centre and the iron ion will donate a electron to the oxygen. In this process, a iron ion has an oxidation reaction, and oxygen has a reduction reaction. A dative bond is formed between oxygen and iron ion.

From the illustration of Schaller C. [4], when heme is binding with oxygen, a relatively stable bent shape with an angle about 120° will occur in the structure, which means it is able to carry oxygen smoothly.

However, the combination with oxygen for heme sometimes can be affected by carbon monoxide since carbon monoxide has a high affinity to the heme in hemoglobin. In the aspect of HOMO and LUMO orbitals in carbon monoxide as demonstration in Figure 5, the molecular orbital in carbon monoxide is full in the σ orbital domain of HOMO, while the π orbital domain of LUMO is empty. From Kong and Crimmin [5], these orbitals, HOMO and LUMO, are two molecular orbitals can respectively act as donating π-donating, which is the empty orbital that iron ion gives to the carbon monoxide and another one is electron-accepting, which is an orbital for carbon monoxide to accept a pair of electrons from σ orbital in iron ion, thus forming a strong double bond Fe = C = O.

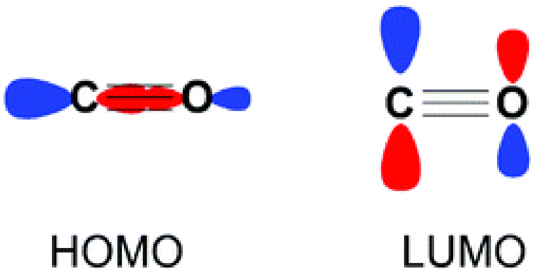

Figure 5. Frontier molecular orbitals of CO depicted as combinations of their constituent atomic orbitals. A second degenerate LUMO orthogonal to the plane of the page is not shown for clarity.[Picture] Royal Society of Chemistry. Source: Kong, R. Y., & Crimmin, M. R. (2020, December 8). https://doi.org/10.1039/d0dt01564d

Other extra conditions can also affect the affinity of heme in hemoglobin to bind with oxygen. "The Bohr Effect refers to the observation that increases in the carbon dioxide partial pressure of blood or decreases in blood pH result in a lower affinity of hemoglobin for oxygen." (*Bohr Effect* | Pathway *Medicine*, n.d.)[6]. With reference to Figure 6 and Pathway Medicine, temperature and blood pH have significant impacts to the affinity. This phenomenon is also famous as Bohr effect.

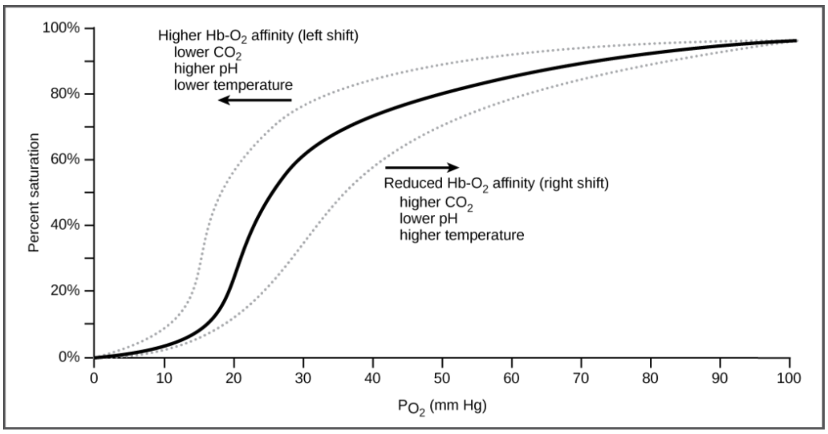

Figure 6. Lumen Learning & OpenStax. (n.d.) The oxygen dissociation curve[Graph]. Source**:** https://courses.lumenlearning.com/wm-biology2/chapter/transport-of-oxygen-in-the-blood/

4. Heme-dependent enzymes

There are a number of enzymes which contain heme groups within them. Catalase enzyme, which is known as a catalyst in the transfer of hydrogen peroxide into water and oxygen, is a typical example of heme-dependent enzyme. "Catalase is a tetrameric enzyme containing four polypeptide chains and a heme group with 4 iron molecules. Heme group allows the catalase to react with peroxide in the first

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place. " (n.d.)[7]. The special heme group with four iron irons in catalase enables it to accelerate the reaction immediately. Other heme-dependent enzymes like peroxidase react in a similar mechanism like catalase [8]. Figure 7 demonstrates the resting state of heme peroxidase.

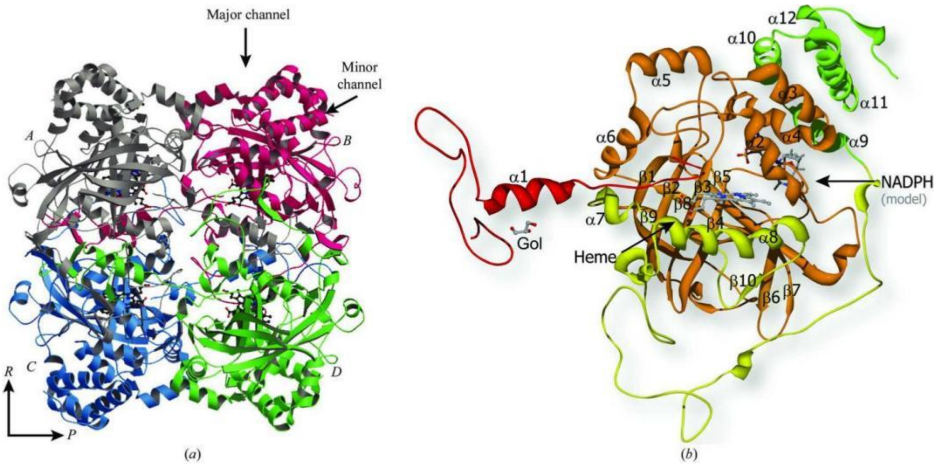

Figure 7. ResearchGate (n.d.) Resting state of heme peroxidases.[Picture]. **Source:** https://www.researchgate.net/Figure/Resting-state-of-heme-peroxidases-In-the-majority-of-cases-L-constitutes-a-histidine_fig1_241862832

5. Other Functions of Heme in Daily Life

Hemoglobin and myoglobin are two proteins that contains heme groups. The former is in charge of transporting and facilitating oxygen within body tissues for human by heme groups. The latter one is a respiratory pigment which has a strong affinity for oxygen than haemoglobin. Myglobin stores oxygen for the respiration needed to keep the heart contracting regularly. All these proteins need heme to maintain their functions. "When oxygen levels are low, myoglobin releases oxygen into the muscles, so they can continue to function. When oxygen levels are high, hemoglobin binds to oxygen and transports it to the tissues and organs that need it." [9]. Myglobin is a great storage of oxygen in human body tissues; it can be an alternative supplier to provide oxygen to human body.

6. Conclusion

Overall, heme is an essential and useful compound in the human body. The synthesis of heme is complicated and occurs in our bodies everyday. The process of binding with gases is the most significant function of heme and how to make substances to help people prevent the priority of binding with carbon monoxide when both carbon monoxide and oxygen occur will be a worthwhile topic for people to explore thoroughly [10]. On another thought, the synthesis process is complex and the binding process is important to every creature throughout the world, which indicates that we should be aware of protecting our heme and its function, preventing it being harmed or losing function. For instance, people need to know that carbon monoxide has a greater affinity than oxygen, so they should smoke less to prevent a low efficiency of respiration.

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