TOWARDS THE ORIGIN OF DARWINIAN NATURAL SELECTION

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(Abstract)

Unless the stipulation of the detailed balance is forcibly imposed on a theoretical ground of whatever type, chemical reactions proceeding there could already be selective internally. What is in place instead is the detour balance that can allow the participation of intermediary reactions in implementing the overall balancing in the involved chemical reactions. The evolutionary nature of chemical reactions in the absence of the detailed balance rests upon the persistent imbalance, even though the slightest one, between a direct pair of the forward and the backward reactions. Some reaction products being set free from the stipulation of the detailed balance can exhibit the chemical affinities that were not actualized in the initial reactants. The lack of the mutual consistency between the reactants and their chemical affinities makes the reactions internally selective and evolutionary, and could have implemented a selective process even prior to the onset of Darwinian natural selection. One likely candidate for constantly breaking the mutual consistency between the reactants and their chemical affinities on the primitive Earth could have been those chemical reactions riding on hydrothermal circulation of seawater around the hot vents in the ocean.

1. Introduction

Significance of Darwinian natural selection cannot be overemphasized from an evolutionary perspective. One witness underpinning the significance is seen in the comment raised by Richard Dawkins on the remark made by Fred Hoyle as stating:

"A junkyard contains all the bits and pieces of a Boeing 747, dismembered and in disarray. A whirlwind happens to blow through the yard. What is the chance that after its passage a fully assembled 747, ready to fly, will be found standing there? So small as to be negligible, even if a tornado were to blow through enough junkyards to fill the whole Universe." [1].

In response, Dawkins made a comment:

"Fred Hoyle was a brilliant physicist and cosmologist, but his Boeing 747 misunderstanding, and other mistakes in biology ... suggest that he needed to have his consciousness raised by some good exposure to the world of natural selection. At an intellectual level, I suppose he understood natural selection. But perhaps you need to be steeped in natural selection, immersed in it, swim about in it, before you can truly appreciate its power." [2].

A key agenda at this point is how we can conceive of natural selection when we refer to it. If one picks up a fossil record over the geological time span, no doubt we could see there an occurrence of natural selection in the products as Dawkins emphasized. Evolutionary products are certainly selective. However, if one focuses upon what is occurring right in the process of natural selection on the spot as Hoyle eloquently called our attention to such a situation, it cannot be subsumed under natural selection in the products. Natural selection in the making is going to act there. It is just more than what natural selection in the products would imply since natural selection in the making does not dismiss from the outset the case such that the process itself, in addition to the products, could be selective. We would need to be steeped in natural selection in the making if it is required to respond to Hoyle's concern more seriously [3].

In particular, any biological organism is in processing an organized assembly of the gene products. Even the most primitive unicellular organism called *Methanococcus* possesses about 1700 gene products of roughly 1.7 million base-pairs length perhaps close to the minimum necessary for supporting living organisms in an independent manner [4]. At issue is a selective nature latent in the organized assembly of the gene products. Both the genes and the gene products are the products of the assembly process. Addressing the assembly products is certainly in accord with differential reproduction of heritable traits, rather than inheritance of acquired traits, because of the built-in stipulation of the gene products following the gene instruction. Nonetheless, the assembly process could maintain some room of exercising a variable selectivity as going through precipitating both the gene products and the genes themselves by means of a DNA replication whose fidelity may not strictly be 100% perfect.

A likelihood of selective capacity latent in assembly process is much broader than what biology may imply, since an organization processing material assembly is also conceivable in the realm of chemistry even without invoking biological processes. A case in point is a set of

chemical reactions involved in forming and transforming the reaction products.

2. Detailed Balance and Beyond

Insofar as chemical reactions are conceived of exclusively within the framework of thermal equilibrium, every forward reaction comes to be balanced with the accompanied backward reaction. That is the principle of the detailed balance. However, once the principle of the detailed balance is faithfully followed, there would be no likelihood of on-going chemical evolution. The balancing between forming the products and transforming the same products into others leaves the resultant reactions in stasis in the sense that there would be no chance of synthesizing new products in the process.

When molecules A and B come to react and form a new molecule A-B by means of a bond-making between the two, the chemical affinity of making an A-B is already latent in an A in isolation and also in a B in isolation. If the reaction of making an A-B from an A and a B satisfies the principle of the detailed balance, the subsequent fate of the product A-B may be made explicit as referring to the further reactions precipitating the consequential derivative products. Although the reactions mediating between the product A-B and the further derivative products are already implicit in the A-B, the chemical affinities latent there are made explicit as referring to the derivative products. What is unique to chemical reactions proceeding under the stipulation of the detailed balance is that all of the relevant chemical affinities are made actual in reference to the existing products. Of course, although there could be a whole array of chemical affinities that may not have a chance of being actualized, those latent affinities would play no significant role within the framework of the detailed balance. The principle of the detailed balance presiding over chemical reactions in thermal equilibrium sets a methodological stipulation of dismissing those chemical affinities not yet actualized as being irrelevant and forcibly depriving the reactions of their evolutionary competency.

The contrast between the actual and the latent chemical affinity is subtle. No one can dismiss the latent chemical affinity in favor of the actual one unless the methodological stipulation of doing so is enforced. For instance, the quantum chemist can correctly and legitimately evaluate the chemical affinity acting between a carbon atom and an oxygen molecule on a theoretical ground. The chemical affinity estimated theoretically is a latent one in the sense that it is relevant only within the attempted theoretical framework. Nonetheless, there is a definite difference between chemical affinities latent in the actual and those latent in theory alone. The difference rests upon who or what is responsible for detecting the molecular participants involved in exercising mutual cohesions between them.

The appraisal of chemical affinities latent in the actual requires the revisiting to chemical reactions in thermal equilibrium. Once the equilibrium temperature is fixed, the decisive factor for determining the ratio of the number densities of the products to those of the reactants in thermal equilibrium is the equilibrium constant which depends only upon the Gibbs free energies of each of the participating reactants and the products. One can find the Gibbs free energy of each molecule involved in the equilibrium chemical reactions unambiguously. However, the prevalence of the equilibrium constants determining the populations of the reacting chemicals may be legitimate only when the equilibrium conditions are kept for the period sufficiently longer than any of the duration time over which the reactants are transformed into the products. If the likelihood of the equilibrium conditions over such a long period is disturbed for whatever reasons, the decisive factor for determining the chemical reactions proceeding there would turn out to be the rate constant of each reaction.

The rate constant is significant in its capacity of referring directly to each individual reaction, whereas the equilibrium constant is relevant only to the population of the reactants in thermal equilibrium. If the issue is about chemical evolution, the role of the equilibrium constant, though which certainly remains legitimate in reaction kinetics in thermal equilibrium, cannot meet the challenge towards addressing evolutionary processes at large because of the imposed methodological stipulation being faithful to the situation in stasis. Once the temperature specifying the environmental conditions is varied for whatever reasons, the role of the equilibrium constant presiding over the reaction kinetics may be marginalized. Instead, the rate constant of each chemical reaction can now come to assume a major role in addressing both evolutionary changes and adaptations as individually regulating the chemical affinities latent in the actual reactants available in the immediate environment.

3. Rate Control and Detour Balance

The rate control of the reacting molecules in chemical evolution would become pronounced in the process of the bond-making between the available small organic molecules and in its consequential hydrolysis. Oligomers or polymers to be synthesized in aqueous milieu are in the interplay between the bond-making and the countering hydrolysis.

When the temperature of the reaction environment is high enough, the reactants can enhance the likelihood of forming a lot of bonds between them as utilizing the heat energy

available there. Then, if the reaction products are suddenly transferred into the cold environment, some of the reaction products can survive the likely hydrolysis of dissociating them back into the initial reactants and can remain as the meta-stable products. The precipitation of the meta-stable products is already selective in that those products that could not survive the hydrolysis were necessarily pruned off. This pruning is undoubtedly rate-controlled in the sense that those products which were faster in their hydrolysis as facing the transference from the hot to the cold environment could not survive there. Once the meta-stable products emerge, the balancing between each direct pair of the bond-making and the hydrolysis is not tenable. What could be possible instead would be the activity for net balancing between a whole set of the bond-making and the hydrolysis being realizable on the level of the population of the participating reactants altogether. That is the detour balance [5].

In addition, what is unique to the meta-stable products in their makeup is that they maintain some remnants of the reactants incorporated in the synthetic reactions that occurred in the high temperature environment just before the products were transferred into the cold environment. The meta-stable products also viewed as the molecular imprints of the preceding synthetic reactions can now extend their own chemical affinities towards the immediate environment. Furthermore, if the meta-stable products can enter the hot environments again as expected in the case of hydrothermal circulation of seawater though hot vents, they can update their makeup in a synthetic manner depending upon the nature of the chemical affinities latent in the preceding meta-stable products and upon the newly available reactants in their immediate neighborhood.

Chemical reactions riding on hydrothermal circulation of seawater through hot vents can thus provide and support those meta-stable products that could update their molecular makeup, though only partially at a time, as repeating the shuttle between the hot and the cold environments. The update of the molecular makeup is nothing other than the molecular exchange being inevitable for supporting the meta-stable products. This view makes a sharp contrast to another view raised by Erwin Schrödinger on the significance of molecular exchange or metabolism as a uniquely biological characteristic as stated below:
"How does the living organism avoid decay? The obvious answer is: By eating, drinking, breathing and (in the case of plants) assimilating. The technical term is *metabolism*. The Greek word (μεταβάλλειν) means change or exchange. Exchange of what? Originally the underlying idea is, no doubt, exchange of material. (E.g. the German for metabolism is *Stoffwechsel*.) That the

exchange of material should be the essential thing is absurd. Any atom of nitrogen, oxygen, sulphur, etc., is as good as any other of its kind; what could be gained by exchanging them? . . . What an organism feeds upon is negative entropy. Or, to put it less paradoxically, the essential thing in metabolism is that the organism succeeds in freeing itself from all the entropy it cannot help producing while alive." [6].

Although Schrödinger declares that the exchange of material should be the essential thing is absurd and that the essential thing in metabolism is that the organism succeeds in freeing itself from all the entropy it cannot help producing while alive, this does not dismiss the case that the exchange of material could be much broader than what metabolism in biology would imply. Rather, once the exchange of material is guaranteed on the physical ground, biology can take advantage of the physical likelihood of metabolism that has already been available, as setting itself free from the additional burden of inventing metabolism for the own sake of biology.

Reaction kinetics undergoing frequent transference of the reactants between the hot and the cold environment such as the one riding on hydrothermal circulation seawater through hot vents can be both selective and metabolic. It is selective even prior to the onset of Darwinian natural selection in pruning off those reaction products that cannot survive hydrolysis when they are suddenly transferred into the cold environments. It is also metabolic even prior to the emergence of the proto-cells in constantly updating the material constituents of the meta-stable products which can survive the hydrolysis when they are transferred into the cold environments as repeating the cycle of the transference between the hot and the old environments. What remains to be seen is the experimental likelihood of processing the meta-stable products.

4. A Case Study; Experimental

When a flow reactor was is utilized for examining the elongation of amino acid glycine into its oligomers as circulating the reaction solution between the hot ($230^{o}C$) and the cold ($0^{o}C$) regions in a cyclic manner, we could observe the exponential build-up of both diglycine and triglycine initially, in which no metallic ions were added into the solution [7]. One possible interpretation of the results is that even if tetraglycine was synthesized in the hot region, it could not survive the hydrolysis when it was suddenly transferred into the cold region with the consequence of being disintegrated into, say, two units of diglycine. Net synthesis of tetraglycine was pruned off. One byproduct of the disintegration into the two units of diglycine could be an exponential growth of diglycine by

repeating the similar visiting to the hot and the cold in a cyclic manner. Once the growth of diglycine happens to be exponential, the similar growth of triglycine would also be likely in view of the fact that the synthesis of a triglycine is due to the bond-making between the dimer and a monomeric glycine. Furthermore, when a diglycine molecule is focused upon, it can be seen as a meta-stable product whose chemical affinity is functional in pulling in the constituent monomers available in the immediate neighborhood for further synthesis of a triglycine or a tetraglycine only temporarily. Monomeric glycine constituting diglycine and triglycine is constantly exchanged with the new one of the same type found in the neighborhood.

One more experimental test for examining the occurrence of the material exchange in prebiotic evolution is a likelihood of running the oxidative citric acid cycle in the absence of biological enzymes in the flow reactor (Figure 1).
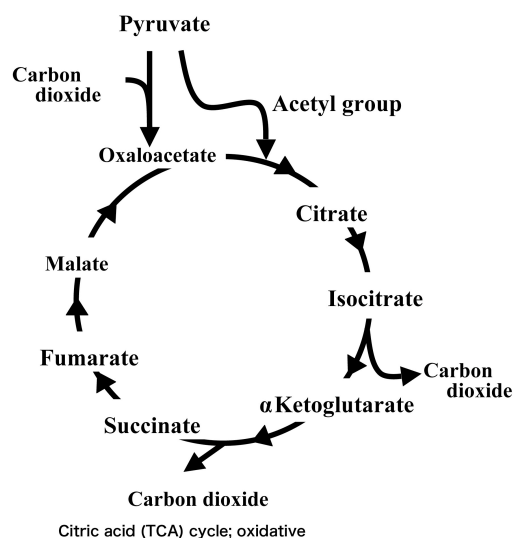

Citric acid (TCA) cycle; oxidative

Figure 1. A schematic diagram of the intended citric acid cycle that is oxidative except for the hypothetical pathway from pyruvate to oxaloacetate due to a possible electrophilic addition of carbon dioxide.

The citric acid cycle as the innermost core member of all extant metabolic cycles [8] runs through either reducing or oxidizing carbon compounds in the cycle. When the earliest organisms were examined, they must have been either autotrophs or heterotrophs. Earliest autotrophs would require carbon to be reduced from carbon dioxide in the atmosphere or in the environments to drive the synthesis of all intermediate metabolites [9], while earliest heterotrophs would require the high concentrations of nutrients such as pyruvate to be oxidized for the sake of extracting energy for running the outer synthetic pathways. This view would suggest an occurrence of autotrophs on the

reductive citric acid cycle [10], while that of heterotrophs on the oxidative one. This contrast between the reductive and the oxidative citric acid cycles, however, raises a serious question of whether the separation between the two could have literally and faithfully been observed even in the actual transition from prebiotic to protobiological evolution [11]. The evolutionary onset of the reductive citric acid cycle would face the problem of how to manage an intricate arrangement of inorganic catalysts so as to prepare and process both the reactants and products at the right places just in time. In contrast, the evolutionary onset of the oxidative one would face the problem of how to synthesize a sufficient amount of nutrients in the absence of enzymes of biological origin.

We then tried to overcome some of the difficulties with each of the reductive and the oxidative citric acid cycles for the sake of getting the cycle started under prebiotic conditions as putting each advantage together in a unifying manner. An important mediator for the unification must be pyruvate. All of the member carboxylic acid molecules constituting the citric acid cycle are on the side of downhill in the thermodynamic energy landscape when viewed from pyruvate [12]. If pyruvate synthesized elsewhere can readily be recruited to the reaction site for its oxidation, the likelihood for initiating the oxidative citric acid cycle may be in sight. In fact, pyruvate can be synthesized from methane thiol as a byproduct of carbonylation reactions at high temperature and pressure sites such as hydrothermal vents in the ocean as using iron monosulphide as a catalyst [13]. The Fischer-Tropsch type reactions near hydrothermal vents are another possibility of synthesizing pyruvate from carbon sources such as formic and oxalic acids [14].

Furthermore, recycling the reaction solution including pyruvate between the high-temperature, high-pressure sites and the cold surrounding water may facilitate the synthesis of mono-, di- and tricarboxylic acids as getting the activation energy from short visit to or near close encounter with the hot sites and quenching the synthesized products rapidly in the cold surroundings in somewhat orchestrated manner [15]. We sought an experimental possibility of the conversion among mono-, di-, and tricarboxylic acid molecules for the onset of the oxidative citric acid cycle in the flow reactor simulating hydrothermal circulation of seawater through the hot vents, under the conditions that pyruvate may be supplied from somewhere else.

We used a flow reactor simulating a hydrothermal environment in the primitive ocean [16], and examined how the reaction solution including pyruvate and the member carboxylic acid molecules constituting the citric acid cycle, namely, oxaloacetate, citrate, isocitrate, alpha

ketoglutarate, succinate, fumarate, and malate, could react among them through the operation of the reactor. The reaction solution including various carboxylic acids was injected at a flow rate of 10 mL/min from a 15 mL heated chamber at 120°-180^oC and at 15-24 MPa. The reactants passed through a thin nozzle of diameter 0.8 mm into a larger and cooler chamber at 0^oC and approximately the same pressure. Most of the reaction fluid stayed in the large vessels of about 580 mL altogether in stirring conditions at 0^oC. Cycle time of the total volume of fluid (600 mL) was about 60 min, but with stirring the reactants cycled roughly once per minute. The actual cycle time of reactants under stirring conditions was measured by running dye molecules (vitamin B_{12}) as a marker through the reactor. Each run lasted 3 hours and started from room temperature, requiring approximately 30-60 min for the high temperature chamber to reach the designated 120°-180^oC. Sampling of the specimen was done from the low temperature chamber every minute.

We then prepared the reaction solution of 1 mM for each of oxaloacetate, citrate, isocitrate, alpha ketoglutarate, succinate, fumarate, and malate, and 10 mM pyruvate as the carbon source. The present setup was based upon the hypothesis that if a sufficient amount of activation energy is available in the flow reactor operation, electrophilic addition of CO_2 to three-carbon pyruvate may lead to the synthesis of four-carbon oxaloacetate and further addition of a two-carbon acetyl group released from pyruvate to oxaloacetate may lead to the synthesis of six-carbon citrate. Of course, experimental confirmation of the synthesis of oxaloacetate from pyruvate and CO_2 remains to be seen.

The source of CO_2 may be endogenous if the oxidative citric acid cycle is really operative, since two molecules of CO_2 are released during each turn of the cycle; one CO_2 molecule from the reaction pathway from six-carbon isocitrate to five-carbon alpha ketoglutarate and another one from the pathway from alpha ketoglutarate to four-carbon succinate. The whole reactions around the cycle would be network catalytic [8, 10] in the sense that the populations of oxaloacetate and all the other cycle members double with each turn of the cycle if their inevitable degradations [17, 18] are not severely counted.

A main objective of the present experiment was to see whether there could be available an empirically approachable window in which all of the major carboxylic acid molecules constituting the citric acid cycle may increase their populations in time. At the least, if the population of every species of the member carboxylic acid molecules is found positive, the supporting citric acid cycle may turn out to be likely. We then ran the flow reactor under the conditions that the temperature of the high temperature chamber was raised from room temperature up to 120^oC over the first 60 minutes linearly and was maintained at 120^oC since then. We set the high temperature chamber at 120^oC instead of 180^oC and the time interval required for linear temperature increase to be 60 minutes instead of 30 minutes to suppress the contribution of thermal decomposition of the reactants. The results of the experiment over the first 180 minutes are displayed in Figure 2. We independently identified the products with use of both an HPLC and a NMR. The results presented in Figure 2 were reproducible in repeated experiments, especially with regard to the initial buildup of citrate synthesis and the occurrence of anomalous spikes in the concentrations of isocitrate, alpha ketoglutarate, succinate and malate.

Citrate as a key carboxylic acid molecule constituting the cycle was observed to build up at least initially, while its concentration finally started to decrease because of the experimental stipulation of supplying no additional pyruvate in the process except for those prepared initially. In order to confirm the reaction cycle in operation and the associated carbon throughflow running round the cycle, we next ran the flow reactor with the reaction solution with only the seven member carboxylic acid molecules present with the concentration of 1 mM for each molecular species and with no added pyruvate. Figure 3 (left hand side) demonstrates only a slight build-up of citrate, but remained far less significant compared to the case in the presence of added pyruvate. Pyruvate was found indispensable for the proper operation of the reaction cycle in general and for the carbon throughflow running round the cycle for the buildup of citrate in particular.

Furthermore, we attempted to run the flow reactor in which one of the seven member carboxylic acid molecules was missing in the initially prepared reaction solution. The missing carboxylic acid molecule we focused upon was alpha ketoglutarate, while the concentration of the other six member carboxylic acid molecules was maintained at 1 mM for each, along with 10 mM pyruvate. The result was also appended in Figure 3 (left hand side). There was observed no significant build-up of citrate. This observation serves as a testimony to the fact that the build-up of citrate requires an uninterrupted and connected reaction cycle supporting the circulating carbon throughflow round the cycle, which certainly functions as a means of the material exchange. All of the seven-member carboxylic acids in the cycle are meta-stable in exchanging their constituent carbon atoms.

Occurrence of the throughflow running round a reaction cycle is regulative in that any incremental increase in the throughflow may decrease the concentration of an arbitrary reactant constituting the cycle when viewed from the upstream towards the downstream, while it can
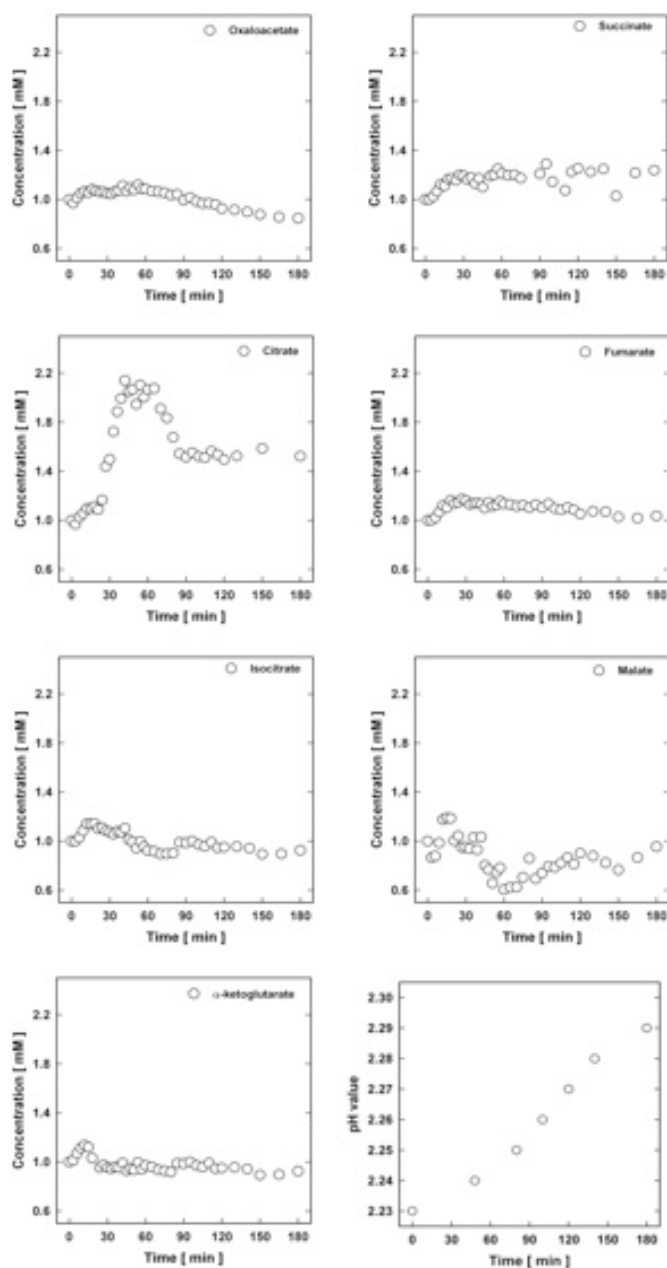
Figure 2. Time developments of the amount of each reactant and the pH value of the reaction solution through the flow-reactor operation, in which the reaction solution was initially prepared at 1.0 mM for each of oxaloacetate, citrate, isocitrate, alpha ketoglutarate, succinate, fumarate and malate, and 10 mM for pyruvate. The temperature of the high temperature chamber was raised from room temperature up to 120°C over the first 60 minutes linearly and was maintained at that temperature since then. The pH of the specimen was measured at room temperature. The observed data included ±1% experimental errors for repetitions for a single run of the experiment. Preliminary results over the first 120 minutes of the reactor operation were already reported in Matsuno and Nemoto [19].

compensate for the decrease when viewed from the downstream towards the upstream. For instance, a slight increase of the carbon throughflow from citrate to isocitrate may decrease the concentration of citrate, while the resulting increase of the throughflow from

oxaloacetate to citrate can compensate for the decrease. The regulative capacity latent in the throughflow now tends to make the supporting reaction cycle robust enough against adverse disturbances coming from the outside to a certain extent. The level of the throughflow has to

internally be determined and to remain somewhat stable against disturbances of external origin, otherwise there would be no likelihood of having such a robust reaction cycle of internal origin.

At the same time, if the reaction cycle is really functional in a robust manner, the cycle itself must eventually be able to help synthesizing and recovering the missing member molecule from within. Otherwise, the robustness of the reaction cycle would have to be lost. We certainly observed that the initially missing alpha ketoglutarate could emerge as a member molecule of the cycle at a later stage of the reactor operation. The synthesis of alpha ketoglutarate became identifiable at about 120 minutes after the start of the operation and its concentration was identified to be about 0.4μM as depicted in Figure 3 (right hand side), and the concentration started to increase since then.

5. Concluding Remarks

Once prebiotic evolution could have reached up to the onset of photosynthesis, the intake of solar photons as the basic resources would turn out to be the decisive factor. What should underlie there must be the faster resource intake, since the slower contender looking for the same resources would have no chance of beating the faster one. A case in point is the light-harvesting antenna for photosynthesis implemented in the Fenna-Matthews-Olson (FMO) protein complex [20].

The FMO complex is in charge of trapping solar photons and transferring the trapped energy in the form of an exciton, or electron-hole pair, down to the reaction center for synthesizing ATP molecules. That is light process in the photosynthetic reaction. Significant in this energy transduction is its extreme rapidity of order of 100 femto seconds or less for its execution with high efficiency [21-23]. If each of the photon antenna, the intermediating exciton, and the reaction center is characterized by its own quantum state independently, expecting such rapidity and high efficiency would be most unlikely. The only alternative is to rely on the scheme that the FMO complex as a whole constitutes a single quantum or equivalently that the three of the antenna, the exciton and the reaction center are coherently entangled quantum-mechanically even at ambient temperatures [24]. Resource exploitation, as in photon capturing in photosynthesis, occurs under the stipulation in irreversible thermodynamics that the faster action takes all, or that 'first come, first served' [25]. In particular, quantum mechanics provides robust material units processing material flows which would feed upon available resources as fast as possible.

Moreover, if one further pays attention to the successive fate of ATP molecules synthesized in light process of the photosynthetic reaction, dark process synthesizing carbohydrates from water and carbon dioxide molecules with the help of the energy released from ATP is seen to follow. That
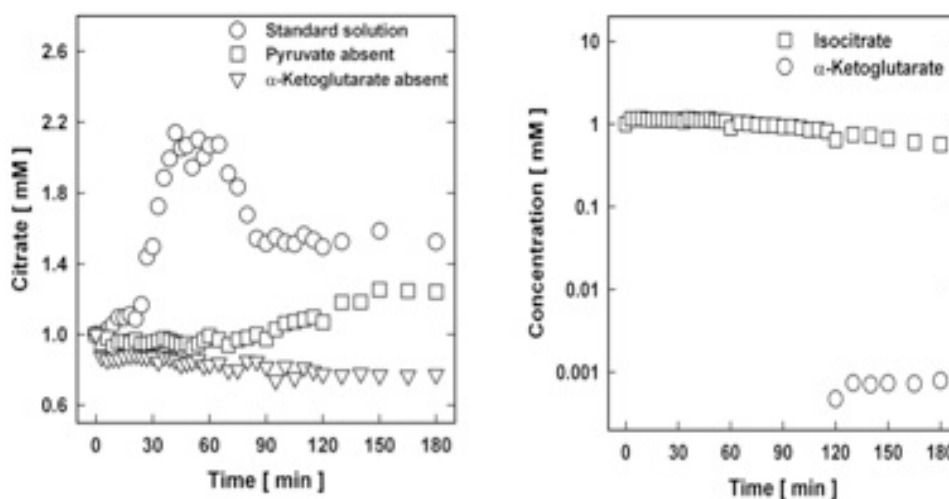

Figure 3. Time developments of the amount of the reaction products synthesized in the reaction solutions. The temperature of the high temperature chamber was raised from room temperature up to 120°C over the first 60 minutes linearly and was maintained at that temperature since then. [Left] Three cases for citrate synthesis were compared. The first one denoted by open circles was for the standard reaction solution consisting of 1.0 mM of each of oxaloacetate, citrate, isocitrate, alpha ketoglutarate, succinate, fumarate, malate, and 10 mM pyruvate in the initial preparation. The second one denoted by open squares was for the reaction solution in which only pyruvate was absent initially compared to the standard one. The third one denoted by open tringles was for the reaction solution in which only alpha ketoglutarate was absent initially compared to the standard one. [Right] Syntheses of isocitrate (open squares) and alpha ketoglutarate (open circles) were compared for the reaction solution differing from the standard one only in that alpha ketoglutarate was absent in the initial preparation. The observed data included ±1% experimental errors for repetitions for a single run of the experiment.

is, the energy transformation from the phosphate bonds of ATP being hydrolyzed to the covalent bonds of the carbohydrates to be synthesized. This energy transformation follows another stipulation that will be registered in the finished record, showing that the most efficient overall reactions will survive over an indefinite period of time, since the less efficient ones become less dominant in succeeding generations in terms of the amount of carbohydrates or the biomass accumulating in the biosphere. 'More of the same' is the principal attribute of the reactions with higher efficiency.

In fact, Darwinian natural selection integrates both principles of "first come, first served" and "more of the same" into the form of differential reproduction of heritable traits. What must be reproduced are the meta-stable products or organizations exchanging the constituent material elements with those new ones found and also available in the immediate neighbourhood. Nevertheless, the metabolic activity is not limited to the biological organisms stipulated by Darwinian natural selection. It is much broader in its implication physically. The present perspective would make the emergence of Darwinian natural selection much easier as taking advantage of the meta-stable products that could be possible and also metabolic even in the absence of prior biological organisms.

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