

Ligand Field Theory and the Origin of Life as an Emergent Feature of the Periodic Table of Elements

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Abstract. The assumption that all biological catalysts are either proteins or ribozymes leads to an outstanding enigma of biogenesis—how to determine the synthetic pathways to the monomers for the efficient formation of catalytic macromolecules in the absence of any such macromolecules. The last 60 years have witnessed chemists developing an understanding of organocatalysis and ligand field theory, both of which give demonstrable low-molecular-weight catalysts. We assume that transition-metal–ligand complexes are likely to have occurred in the deep ocean trenches by the combination of naturally occurring oceanic metals and ligands synthesized from the emergent CO₂, H₂, NH₃, H₂S, and H₃PO₄. We are now in a position to investigate experimentally the metal–ligand complexes, their catalytic function, and the reaction networks that could have played a role in the development of metabolism and life itself.

Background and Significance

Since the postulation of chemical biogenesis by A. I. Oparin and J. B. S. Haldane in the 1920s (Oparin, 1967; Haldane, 1929), the circular reasoning about catalysis has been an ongoing concern. Biological catalysts are macromolecules, made from monomers, that are synthesized by the catalytic action of the macromolecules. This clearly has the character of the problem of which came first, the chicken or the egg. Two somewhat related developments of the last few decades have moved toward resolving this difficulty: the organometallic chemistry of the transition metals (Orgel, 1960; Winter, 1994) and organocatalysis (Barbas, 2008; MacMillan, 2008). In both cases, relatively small structures, less than 500 Da, can serve as catalysts for organic reactions

of the kind used in biochemistry, thus opening the possibility that anabolism of the monomeric building blocks of polymers can proceed without requiring the prior presence of the macromolecules themselves. Both approaches to catalysis have had their main influences in industrial chemistry, bioinorganic chemistry, and pure organic chemistry rather than in biochemistry. The effects of these advances on developments in the origin of life domain have tended to lag behind the progress in the main fields of application. We have previously discussed organocatalysis (Morowitz *et al.*, 2009). We now turn attention to ligand field theory (Gray, 1994; Crabtree, 2009), the theoretical foundation of organometallic chemistry. This discipline utilizes the quantum mechanical foundations of understanding catalysis by transition metals and their ligands and thereby provides a connection with metabolic networks. The theory is thus central to the search for the role of transition metals in both present-day biology and biogenesis.

The underlying theme of this essay is to show that, following from ligand field theory of transition metals and the nature of ligands produced in prebiotic synthesis experiments, life—or at least network anabolism—becomes a plausible emergent feature of the periodic table of the elements. This line of reasoning began when Lawrence J. Henderson authored a book entitled *The Fitness of the Environment* (Henderson, 1913). This work makes a strong case for the necessity of water and the role of certain geochemical and geophysical properties of the planet in the origin and continuance of the life that we know. Some 49 years of continuing work led to the book *Horizons in Biochemistry* that contained an extraordinary chapter by George Wald titled “Life in the Second and Third Periods; or Why Sulfur and Phosphorus for High Energy Bonds?” (Wald, 1962). This chapter is broader than its title and continued Henderson’s work of rooting biochemistry in the core of chemistry,

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the periodic table of the elements. Wald sums up, "There are atoms that form the bulk of organic molecules: C, H, N, and O, and in special instances S and P; there are major monoatomic ions Na^+ , K^+ , Mg^{++} , Ca^{++} , and Cl^- ; there are trace elements, mostly transition elements, and hence adapted to fill the roles in which we mainly find them, as nuclei and ligands in metallo-organic complexes and oxido-reduction enzymes containing Fe, Mn, Co, Cu, and Zn." He proceeds to a detailed discussion of the roles of C, H, N, O, P, and S, and argues why these cannot be fulfilled by other elements for life in an aqueous environment.

As a bit of oral history, one of us (HJM) met Wald at a meeting in 1979, in Dubrovnik. The subject was "Self Organizing Systems, The Emergence of Order." At one of the breaks, I asked him if he and Henderson had much interaction during their 8 years of overlap at Harvard. Indeed they had. Wald was a Nobel Laureate for his work on rhodopsin and vision, and Henderson was a distinguished physiological chemist best known today for the Henderson-Hasselbalch equation dealing with the pH of solutions of weak acids. When I took philosophy of science as an undergraduate, one of my teachers had done his Ph.D. thesis under the joint direction of Henderson and Alfred North Whitehead. Feeling some connection, I asked Wald what he could tell me about Henderson. He reported that the savant has a large red beard and a forceful oratorical style, leading some of his students to refer to him as "the pink Jesus." After the meeting in Croatia, Wald was off to his own spirituality, spending some time in an ashram in India.

What Wald was attempting—an approach that we follow—was to map biochemistry onto the underlying quantum-mechanical logic of chemistry as exhibited in the periodic table of the elements. Thus we briefly consider the structure of the periodic table in terms of electron orbitals (Pauling, 1947). One filled orbital exists for each proton in the neutral atom, adding up to the atomic number. As a consequence of the solution of the Schrödinger equation (at first approximation treating complex atoms as if they were hydrogen atoms with higher charge but without electron-electron interactions) and the Pauli exclusion principle, each orbital is indexed by four quantum numbers, and no two electrons in an atom can have the same four. The principal quantum number 'n' is the major determiner of size and energy. It also determines the row of the periodic table. The total orbital angular-momentum quantum number, 'l', designates the value of the angular momentum of the electron and may have values from 0 to n-1. The third quantum number—which can be made to correspond to the projection of the angular momentum onto any single Euclidean axis and is known as the magnetic quantum number—has values from -1 to 1 but does not enter in the energy in the absence of a magnetic field such as that used to produce the Zeeman effect. The fourth, or spin magnetic quantum number, can have values of 1/2 or -1/2. By the Pauli exclusion

principle, a fully specified orbital with assigned values for all four quantum numbers can never contain more than one electron.

Shells of orbitals having 'n' equal to 1, 2, 3, 4 are designated respectively K, L, M, N. Total orbital angular quantum numbers, counting upward from zero, are designated s, p, d, f. Thus for 'n' equals one, l can only equal zero and the only possible spatial orbital is labeled 1s. For 'n' equals 2 and l = 1, the orbital magnetic number can be -1, 0, 1, corresponding to the labels 2px, 2py, 2pz. For 'n' equals 3, the 'd' orbitals (l = 2) enter, with magnetic quantum numbers of -2, -1, 0, +1, +2. Allowing for electron spin, there are 10 such 'd' orbitals. The first period n = 1 consists of hydrogen and helium. The second period n = 2 includes lithium, beryllium, boron, carbon, nitrogen, oxygen, fluorine, and neon. As Wald (1962) points out, hydrogen, carbon, oxygen, and nitrogen are the core elements of biochemical structure. The row structure of the periodic table becomes complicated in relation to the quantum numbers, in that the '3d' orbitals come to be filled after the '4s' and '4p,' so that in order to describe l = 2 angular momentum, we must look in the fourth rather than the third period.

We therefore turn attention to the transition elements, or transition metals, which Wald mentions in passing. They are characterized as having atoms or ions with incomplete or complete shells of 'd' orbitals; the ones we are most interested in are groups 5 to 12 in the fourth period and molybdenum and tungsten in the next periods. They are part of a cluster of the periodic table called the 'd' block elements/chemicals. In present day biology they form a very small part of the mass of functioning cells, usually less than 1%, yet they play a central role as cofactors as well as essential components in perhaps half of all proteins. The best studied for their biological roles are vanadium, manganese, iron, cobalt, zinc, molybdenum, copper, and nickel.

As we noted, transition-metal complexes, or 'd' block complexes, consist of a central transition-metal atom or ion surrounded by molecules and ions, usually nonmetallic. When these surrounding structures are bonded or otherwise attached to the metal, they are called *ligands*. This is a restricted use of the word *ligand* used in ligand-field theory, which deals with molecular orbitals and bonding of the metals and ligands. *Ligand* in present-day biochemistry often refers to any molecular grouping that attaches to a protein. A special, and for our purposes a very important, feature of transition-metal complexes is that they are often catalysts. As Crabtree (2009) noted, "Main group organometallics are normally stoichiometric reagents, but transition-metal organics are typically catalysts." It is this feature of transition-metal organometallics that renders them so significant in biogenesis. They provide the necessary catalytic ability to generate the reaction networks and the core molecules of autotrophic intermediary metabolism that are

themselves particularly facile and catalytically efficient ligands, potentially overcoming the chicken-and-egg conundrum.

Ligand field theory is the application of molecular orbital theory to the complexes described above. All of quantum chemistry begins with the solution of Schrödinger's equation for the hydrogen atom (Pauling and Wilson, 1935). As we have noted, a set of four quantum numbers then designates an atomic orbital. For atoms with more electrons than hydrogen, complications arise. Exact solutions are not possible and various approximations are introduced; these still index orbitals with four quantum numbers representing the rotation group in space and in spin, but they allow for more complex many-electron representations. In molecular orbital theory, psi functions are regarded as associated with bonds rather than atoms. In ligand field theory, orbitals are associated with the entire complex, thus allowing for more chemical subtlety. The orbitals are still weighted sums of atomic orbitals, but the s,p,d overlap renders the probability functions more global over the entire complex.

Ligands in general bring two electrons to the metal-ligand interaction, and the binding is said to be *dative* or *coordinate*. Thus the complex has a certain unitary character, as if it were represented by a psi function for the entire collection of atomic centers. The contributing bonds when viewed separately may have characteristics of sigma, pi, and ionic bonding. Over the entire complex they have something of the feature of metallic bonds with a certain mobility to the electrons. This might show up in the dielectric dispersion studies of suspensions of complexes.

Ligands in general may attach to the metals with coordinate bonds involving the lone pair of electrons in :O, :N, or :Cl⁻. The ligands may attach at one or more atomic orbitals of the transition metal. As many as nine attachments are possible owing to the 2s, 6p, and 10d orbitals (18 electrons leading to 9 coordinate bonds). Ligands may attach at one site (monodentate), two sites (bidentate), three sites (tridentate), and so on up to a structure like rhenium with nine hydrogens and a charge of 2 minus. Polydentate ligands are chelators and may act to solubilize transition metals. For example, citric acid is used in cleaning solutions because with three or four possible attachment sites it effectively solubilizes some transition metals. The most common complexes have a single transition metal and six ligands or ligand sites. The hexadentate EDTA (ethylenediaminetetraacetic acid) is widely used as a water softener and metal solubilizer.

The transition metal atom and its ligands are a single structure whose properties are governed by a single psi function that may be approximated by molecular orbital theory. The permanence or lack of permanence of the complex may be determined by the thermodynamics of their interaction, as pointed out by Yatsimirskii and Kozachkova (2005). Their rather detailed study discusses "Thermody-

amic parameters of the formation of 3d transition metal complexes as model systems for description of substrate-receptor interaction." We note their abstract:

The thermodynamic characteristics of doubly charged ions of 3d metals with ligands containing oxygen, nitrogen, and fluorine donor atoms are analyzed. The complexing reactions are separated into three main groups on the basis of the changes in the enthalpy and entropy components of the Gibbs free energy. It was shown that the assignment of a reaction to a particular group is determined by the nature of the donor atoms in the ligands. (Yatsimirskii and Kozachkova, 2005)

Thermodynamic values are given for manganese, iron, cobalt, nickel, copper, and zinc, and range from 1 to 116 kJ/mol, largely dependent on the polydentate values of the ligands and the softness and hardness of the interactions. The largest value is for the hexadentate EDTA. Among the ligands reported are the dicarboxylic acids, malonic and succinic. What is clear is that aqueous mixtures of transition metals and ligands will have an equilibrium shifted to the side of complex formation.

Malonic and succinic acids are members of the core anabolic metabolism. In general, if one looks at the intermediates in the network of anabolism of autotrophs (Srinivasan and Morowitz, 2009a), many are effective ligands. This is because of the presence of carboxylic acids, phosphoric acids, amines, sulfhydryls, and imidazoles in the metabolic network (Srinivasan and Morowitz, 2009b). Now, the set of metabolites of autotrophic metabolism overlaps heavily with the molecules formed in experiments looking for prebiotic synthesis, suggesting a possible role of metal-ligand structures in biogenesis. Related metabolic structures have been pointed out (Srinivasan and Morowitz, 2009b), suggesting that metal-ligand complexes are plentiful in the waters of the world's seas.

Next consider ligand-metal complexes in water. Water molecules themselves may be ligands because of the unbonded electron pair on the oxygen. If one or more of the ligands has an acid-base dissociable group, the complex is sensitive to the pH of the medium. If one or more of the ligands has an oxidation-reduction active group, the complex is sensitive to the redox environment. Given hydrogen bond sites on the ligands as well as nonpolar groups, the complex can be affected by the concentration of certain solutes and can bind onto them. Each one of these actions will feed back with great speed on the global psi functions and will affect what is going on at other ligands in the complex.

The features stated above address the question of why incorporation of transition metals leads to good catalysts. An online publication raised this issue. We can do no better than quote the author's answer.

Complexation by transition metals affords access to a wide variety of oxidation states for the metal. This has the property

of providing electrons or withdrawing electrons from the transition state of the reaction (transition state not to be confused with transition metal). That is, if the transition state is electron rich, then the transition metal might hold some of the electron density and thus prevent too much from building up on the reagent. This would then facilitate the reaction. Or the transition state might undergo formal oxidation/reduction to achieve electron transfer to the substrate, thereby allowing a reaction to occur. This is complexation and electron storage taken to the extreme, but a common mechanism in organometallic chemistry. It is the ability of the transition metal to be in a variety of oxidation states, to coordinate to a substrate and to be a good source/sink for electrons that makes transition metals such good catalysts. (Whitecombe, 2000)

In this sense biochemistry merely uses and controls an emergent feature of the periodic table expressed at the molecular level, without needing to create it from novel structures. The affordance that such chemical features give to life makes its emergence more plausible as a necessary outgrowth of astrophysics and geochemistry.

The possible role of transition metals in biogenesis was suggested early on (Beck and Ling, 1977) in an article with the intriguing title “Transition metal complexes in the prebiotic soup.” A group of books prior to 2000 on the origin of life barely made mention of the role of transition metals (Shapiro, 1986; Morowitz, 1992; Lahav, 1999; Fry, 2000). Wächtershäuser and coworkers in the 1990s (Wächtershäuser, 1992; Huber and Wächtershäuser, 1988, 1997) studied prebiotic chemistry and transition-metal complexes with particular attention given to iron sulfides. They noted that “with the pioneer organism begins a primary direct process of evolution. It is chemically determined and directionally fixed by the universal laws of carbon fixation on transition metal catalysts.” Starting around 2000, Cody and coworkers (Cody *et al.*, 2000) have reported on experiments with transition metals with a similar focus on iron sulfide as well as other metals. More recently there has been a consideration of transition metals with respect to chemiosmosis (Nitschke and Russell, 2009). These studies have tended to support the metabolist view of life’s origin. In any case, there has been a developing body of theory suggesting that special properties of metals and their ligands provide the catalytic thrust necessary to generate a metabolome. To make a metabolome, non-equilibrium chemistry requires the informatic loop to lead to network autocatalysis.

The early ocean presumably contained transition metals in concentrations from 0.03 to 10 parts per billion (Fraústo da Silva and Williams, 2001). The environment was anaerobic. Also in solution were small molecules synthesized from high-temperature emissions from the magma (Cody *et al.*, 2000). These tend to be ligands, often bidentate and higher, making them excellent chelating agents. In this perspective, rather than a solution of metal ions and small organics, the aqueous medium contained complexes of tran-

sition metals with one to six ligands. The two views of the prebiotic ocean are very different. The ligand-field view fills the ocean with catalytically active complexes. Energy was supplied by the chemical potential of the magma and magma-derived solids. Energy flow drove the processes. It was a sea of gadgets rather than a broth. Given the number of transition metals, the number of allowable redox states, and the number of ligands in the core metabolic network, a substantial and sophisticated array of catalysts is possible.

In present day biochemistry, transition metals are perhaps best known as cofactors with tetrapyrroles or porphyrins (Begley, 2006). The most potent and best known of these involve iron, cobalt, nickel, and magnesium (although magnesium is not a ‘d’ block element). These metals are generally coordinated to four nitrogen atoms, one from each pyrrole. The directionality of the coordinate bonds is an important feature in the structure of hemes, cobalamins, chlorophylls, and related structures. At the next level, a large number of proteins contain transition metals held by the ligand activity/ability of amino acid side chains (Lippard and Berg, 1994). These metals may be involved in tertiary structure or may be a part of catalytic active sites. Thus, over the entire ecosphere, transition metals play distinct roles in structure and function for which they may be essential.

However, the role is often difficult to ascertain in part because of their presence in such low concentrations. The concentrations observed are highly variable, ranging from that in ascidians or seascorps, who concentrate vanadium over 10 million times that in seawater (Silva and Williams, 2001), to some transition metals found in living tissue in only femtomolar concentrations. They may be present near the limits of analytical detection. One would have suspected that iron, because of its apparently essential role in cytochromes, would be universal, yet the fermentative taxon *Lactobacillus* seems to function with no iron.

Escherichia coli, on the other hand, pumps out an elaborate system of siderophores to pick up iron atoms, which are then actively transported into the cells. Cobalt, the core transition metal of cobalamin (vitamin B12) is an absolute requirement for mammals to prevent the potentially lethal pernicious anemia, yet is not required by plants. One would suspect that zinc is an absolute requirement for its role in protein structure, but this has not been firmly established for all taxa.

Position Summary

The conjecture we are setting forth is as follows:

1. The early oceans and bordering lithospheric components contained transition metals in solids or in aqueous components ligated to H₂O, CO, CO₂, NH₃, and sulfur in various oxidation states.
2. The emerging CO₂, H₂, NH₃, and polyphosphate,

driven by thermal energy or chemical energy, gave rise to additional small molecules that served as more sophisticated ligands to complex with the transition metals.

- Several of these complexes possessed catalytic ability, leading to a kinetic organization of the resultant network of possible synthetic reactions.
- This initial network gave rise to a network with an autocatalytic loop such as the reductive tricarboxylic acid cycle (Smith and Morowitz, 2004).
- The rest is history constrained by the laws of physics and chemistry.

This conjecture is subject to testing in the following ways:

- Choose the most likely group of 'd' block elements.
- Consider the most likely ligands/compounds from the canonical chart of autotrophic anabolism (Srinivasan and Morowitz, 2009b). There are 125 to choose from.
- Make up arrays of mixtures.
- Test the mixtures for catalytic functions, using the known catalytic processes from contemporary biochemistry (Petsko and Ringe, 2004; Fersht, 2009). These tests are to show that the schemata are within the domain of experimental biochemistry. The last paper of Orgel (2008) lays out an ideal sequence of organic reactions at the core of biochemistry, which provide relevant first targets to test for catalytic efficacy and specificity.
- Using the results of the experiments for guidance, formulate sets of molecular orbitals appropriate to the questions under consideration (Eyring *et al.*, 1944).

We believe that by combining known principles of ligand-field theory with new insights into organocatalysis and organo-metallic catalysis, the question of whether intermediary metabolism is a deterministic emergence from the periodic table of the elements can be systematically addressed in a series of laboratory experiments.

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