J. Mol. Evol. 11, 163–169 (1978)

Journal of Molecular Evolution


# Bioorganic Chemistry and the Origin of Life

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**Summary.** A challenging theme in bioorganic chemistry is the unification of established theories of biochemistry and organic chemistry to provide new patterns for interpretation and experimentation. Especially relevant examples of such interactions can be drawn from the field of enzyme catalysis and, in particular, the role of cofactors therein.

Knowledge of the chemical mechanisms by which some of the cofactors function has progressed rapidly with the aid of studies of the cofactors themselves (or compounds of related structure, "models") stripped of the accompanying apoenzyme. The striking successes in this field likely arise from a fundamental resemblance between bioorganic chemistry (especially coenzyme models) and chemical evolution before the appearance of coded polypeptide enzymes.

**Key words:** Bioorganic Chemistry – Origin of Life – Cofactor Models – Chemical Evolution

## A Borderline Science

Bioorganic chemistry is a young and rapidly growing science arising from the overlap of biochemistry and organic chemistry. Particularly in the field of mechanisms for enzyme catalysis – at the moment the main area of overlap – remarkable progress has been made. For some hydrolytic enzymes the catalyzed reaction has been translated already into a series of "normal" organic reaction steps. At the same time organic chemists are imitating the characteristics of enzyme catalysis in model reactions dealing with both the rate of reaction and specificity.

A new borderline science is not constructed from a few axioms but grows more or less spontaneously as the interaction between the overlapping disciplines grows. It is of little use to try to define precisely such a new specialty, but some reflection upon it is needed because of frequent careless use of the word "bioorganic" and because a framework for problem analysis must be built.

0022–2844/78/0011/0163/$ 01.40

Historically, the classical chemistry of natural products with its characteristic triad of isolation, structural proof and total synthesis is an evident, but purely organic ancestor. Likewise, inquiry into the biosynthetic pathways for the same natural products is plain biochemistry. But when the total synthesis of a neutral product explicitly is based upon the known route of biosynthesis or if the biosynthesis has been translated into structural and mechanistic organic chemical language, one is clearly dealing with bioorganic chemistry. An early example of the first type of interaction is the well-known biogenetic type tropinone synthesis developed by Robinson (1917a). An equally old example of the second type is found in the same author's ideas (1917b) in the alkaloid field. Current examples wherein biochemical knowledge, methods and ideas are directly applied within organic chemistry, are illustrated by:

– *Biomimetic chemistry*, a branch of organic chemistry wherein the object is to mimic natural reactions and enzymatic processes in order to get a better organic synthesis. "Better" stands here for faster and particularly for more specific. A good example is recent work of Breslow (1972, 1973 and 1974), on means of functionalizing saturated steroids specifically.

– Applications in *pharmacology*; designing drugs that inhibit a simple enzyme specifically, an example being the transition state analogs (Lindquist, 1975).

– A third example of biochemistry, applied to organic synthesis can be found in the growing field of *enzyme technology* (Skinner, 1975).

A second type of bioorganic chemistry can be described as organic chemical knowledge, methods and ideas, necessary or useful for understanding the chemical aspects of life and its origin. At this point a definition of what "life" is from a chemical point of view would be useful, but this is difficult to give (Monod, 1970). Phenomenologically, the most characteristic of terrestrial life is, in our opinion, the combination of the following two processes:

– heredity, which means storage, transfer and expression of genetic *information*, with the underlying principle of *paired* organic bases, and

– storage, production and use of *energy*, with the possible underlying principle of – recently proposed by Blondin and Green (1975) – *paired* moving charges.

Both processes together form metabolism, an *intricate and strongly ordered* system of chemical reactions, regulated by their catalysts, which are *intricate and strongly ordered* amino acid polymers. This central position of the enzymes in the living cell makes it understandable that research on the mechanisms of the enzymatic reactions presently takes a central place in this second type of bioorganic chemistry.

It becomes steadily more customary to analyze possible mechanisms on the basis of fairly simple organic chemical models that combine only the more fundamental factors of the enzymatic catalysis. Starting from established reaction theories from both biochemistry and organic chemistry one tries to reconcile two ways of thinking in order to get new insight into what life is. The method itself, this roundabout way via relatively simple models, often leads to the surprising consequence that the problem of the origin of life emerges. The border between organic chemistry and biochemistry is man-made and systematic. This border is related closely to the historical transition between non-living and living. Some initial remarks concerning recent developments in the thinking about the origin of life, the "bioorganic era", therefore, are in order.

**Entropy, Life, Evolution**

In the middle of the last century two principles were formulated almost simultaneously. Both were fundamental to scientific thinking and had far-reaching consequences outside science (philosophy, theology). The principles were in fact diametrically opposed.

In classical thermodynamics it was the second principle (Carnot-Clausius), implying that in every spontaneous process the entropy increases, or, put otherwise, that structure decreases. Applying this principle to our world as a whole suggested that life as we now know it must be the result of a still more structured "higher" life in a dark and distant past. In short, "gefundenes Fressen" for theologians. The second principle, Darwin's theory of evolution, implied on the contrary a very gradual build-up of structure during biological evolution. The discussion around these two conflicting theories has lasted up to our time (Heitler, 1961) and ended ultimately with the development of the thermodynamics of irreversible processes, chiefly by Prigogine and collaborators (Prigogine, 1967; Glansdorff and Prigogine, 1971). The outcome was that the two conflicting principles are valid and opposite indeed but do not apply simultaneously. Both have their own spheres of validity: respectively near and far from thermodynamic equilibrium. Near equilibrium the second principle holds and entropy increases in every spontaneous process. Processes far from thermodynamic equilibrium on the contrary can build up structure spontaneously, depending on the boundary conditions. The two areas of validity do not overlap, but are sharply separated. Historically, the extension of classical thermodynamics to open systems far from equilibrium took place in two stages.

The first stage was the extension of classical thermodynamics to thermodynamics of linear irreversible processes. In an isolated system (no exchange of heat or matter) the entropy is *constant* and *maximal*. A stationary irreversible process (not an isolated system, that means closed – only exchange of heat – or open) must therefore continuously produce entropy. The criterion for stability of such a stationary process now is that the *rate* of entropy production is *constant* and *minimal*. The magnitude is directly dependent on constant forces applied from the outside (Prigogine, 1945). A stationary irreversible process "strives" toward minimal entropy production. Every small disturbance of the process means increasing the rate of entropy production and will be acted against (principle of Le Chatelier-Braun). This first extension of the second principle of thermodynamics "explains" the existence and the stability of a living (adult) organism.

"A living organism eats negative entropy" (Schrödinger, 1956). The theorem of minimal entropy production can also be applied to processes with other time-scales such as for instance biological evolution (origin of species) (Prigogine and Wiame, 1946). A species will develop – in size, form and kind of metabolism for example – in such a way that its need for negative entropy is minimal.[1] The condition for applicability of the theorem is that the process is not far from thermodynamic equilibrium and that the forces from outside are approximately constant.

The second stage was the extension of the second principle to the thermodynamics of non-linear (far from equilibrium) irreversible processes (Glansdorff and Prigogine,

[1]Prigogine calls this a "Lamarckian" element in evolution.

1971). This ultimate stage of generalization consists of a more general stability criterion for spontaneous processes. In classical thermodynamics the pivotal figure is the amount of entropy, and in linear thermodynamics of irreversible processes, it is the rate of entropy production, the first derivative of it. The general criterion however is expressed with a second derivative, the rate of change of the rate of entropy production. That figure is positive for each stable process, far from or near equilibrium but decreases on growing distance from equilibrium. Sufficiently far from equilibrium it becomes zero, which means that the process has become unstable. The system can then spontaneously change into a new regime and by doing so build up structure in time and/or space. Structures, arising in that way, in non-linear processes far from equilibrium are called *dissipative structures* (Prigogine and Lefever, 1971; Prigogine and Lefever, 1973), opposed to *equilibrium structures* which can arise and exist in reversible processes (crystals for instance). In the case of chemical reactions the condition sufficiently far from equilibrium can be fulfilled by continuous and effective removal of a product or by an autocatalytic step in a reaction sequence. Both situations are frequently encountered with enzymatic reactions (Prigogine and Babloyantz, 1972). An example of an organic chemical system that spontaneously builds up a dissipative structure from a homogeneous solution is the well-known reaction of Zhabotinski (oxidation of malonic acid with $Ce^{4\oplus}$-ions) (Herschkowitz-Kaufman, 1970). The theory can also be applied in biology (Prigogine, 1972). The boundary between the two thermodynamic situations, wherein the increase in rate of entropy production is zero, is the border-line between a domain wherein structure spontaneously vanishes and a domain wherein structure spontaneously arises (at the expense of energy). The existence of such a discontinuance in the validity of two complementary fundamental principles appears at first sight strange, but is in many respects comparable to the "normal" transition between two phases in classical thermodynamics. In short, classical thermodynamics can be seen as the theory of vanishing structure, the first extension to linear irreversible processes as that of existing structure, and the second extension as that of arising structure. With the help of this generalized thermodynamics it is possible to redefine Darwin's principle (survival of the fittest) and to apply it to prebiological evolution (Prigogine et al., 1972). With this a one century old controversy ends in the reassuring conclusion that life could arise. But the theory is also important for the formulation of models showing the inevitability of the prebiologic evolution, not in a deterministic, but in a stochastic sense (Eigen, 1971; Kuhn, 1976a and b). How far it will turn out to be possible to trace back the *historical* course of events can not be said at this moment.

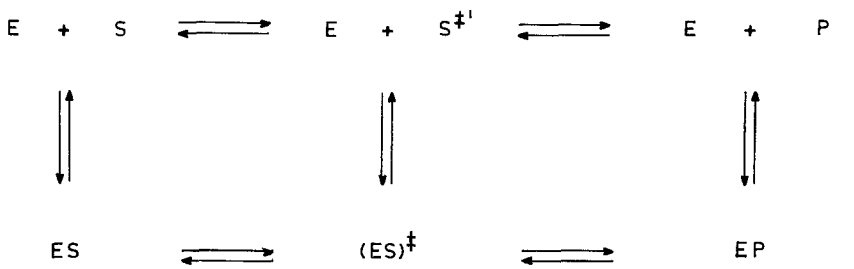
**Models for Enzyme Catalysis**

Although the problems connected with the origin of life remain truly formidable, we nevertheless believe that there must have been a gradual evolution – continuous, in phases or by little leaps – of life from non-living matter. Historically there has not been a sharp borderline between living and not yet living. Maybe this is the basis of the intuitive starting point of bioorganic chemistry, namely that there is no essential difference between enzymatic reactions in living organisms and "simple" organic chemistry. It is therefore possible and useful to approximate the intricate enzymatic

process with chemical models. This intuitive starting-point is implicitly present in different ways in much bioorganic literature. Three examples: First, "the more an (enzymic) system is stripped to its simplest components, the more closely it will resemble an older and more fundamental stage", a rationalization often hidden in the word "primitive" used in this context. It consists in the coincidence of a logical and a historical sequence and is typical of every evolutionary idea. An enzymatic reaction may stem from a spontaneous chemical reaction that through evolution has been speeded up and made more selective through development of a sophisticated enzyme catalyst. But the basic chemical reaction being catalyzed has remained unchanged during the course of evolution. This train of thought has been used to explain the success of some models for enzymatic reactions (Kellogg, 1975). Second, "the more general a biological system, the older and the more fundamental". One example of this idea is the reconstruction of the course of biological evolution from similarities and differences in amino acid sequences of one particular enzyme in all the still existing species (Schoffeniels (ed.), 1971; Bryson and Vogel, 1965).

Organic chemistry, as shown in metabolism, is remarkably constant through the whole of terrestrial life, although there is a great variety in species and within a species. Within a particular enzyme a great deal of variation is encountered, but coenzymes are alike for all living systems. This suggests again that the chemical reactions and the manner by which they are catalyzed during the period in which life arose and also thereafter is a fairly constant datum. The transition state of an enzymatic reaction (the structure of the substrate in the activated complex) and that of the non-enzymatic reaction are according to this idea approximately equal. This corresponds to the earlier mentioned transition state theory for enzymatic reactions, recently developed from an older idea of Pauling (1948). This theory (Lienhard, 1973; Wolfenden, 1972; Jencks and Page, 1972) forms the third example of the implicit starting-point of the bioorganic chemist. In this theory an enzyme is simply described as a polypeptide with an active site that is complementary to the transition state of the reaction to be catalyzed. This complementarity causes maximal bonding of the transition state and thereby maximal stabilization. Both increase of the reaction rate and substrate specificity are explained in this manner. Hence, there is no need for great mobility between different conformations of the enzyme during the reaction. Applications in pharmacology, until now the greatest area of success of the theory, have already been mentioned. For the simple case of a one substrate reaction (a racemization for instance) the following scheme can be defined, eq. (1).

non-enzymatic reaction




enzymatic reaction

in which E = enzyme; ES = enzyme-substrate complex
S = substrate; $S^{\ddagger'}$ = transition state non-enzymatic reaction.
P = product; $(ES)^{\ddagger}$ = transition state enzymatic reaction.

To compare the two transition states, it is useful to divide the equilibrium for complexation of E and $S^{\ddagger'}$ in two equilibria:

$$E + S^{\ddagger'} \rightleftharpoons E + S^{\ddagger} \rightleftharpoons (ES)^{\ddagger}$$

in which $S^{\ddagger}$ stands for the structure of the substrate portion of $(ES)^{\ddagger}$. The present state of knowledge about the transition state on the enzyme suggests that there is a fundamental similarity between the enzymatic and the non-enzymatic reaction regarding the processes of bond breaking and bond making that S undergoes on its reaction path to P (Jencks, 1969; Bruice and Benkovic, 1966). This means that there are at this moment no known exceptions to the rule that $S^{\ddagger'}$ and $S^{\ddagger}$ are similar in structure and energy. In general it must hold that the energy of $S^{\ddagger}$ is equal to or is higher than that of $S^{\ddagger'}$, because all reactions – also those not catalyzed – go along the reaction path with the lowest activation energy. It is of course always possible that $S^{\ddagger}$ lies considerably higher in energy than $S^{\ddagger'}$, but this is a priori less probable because enzymes have *evolved* as substances that *lower* transition states (Lienhard, 1973). So, this third consideration, just like the first two, is based upon the a priori assumption that life arose in an additive evolution, in the sense that the organic chemical processes present on the earth before life existed have been preserved in good approximation. The validity of this assumption remains, however, to be proved, because an opposite standpoint, although seemingly improbable, is not impossible. Especially in the beginning of the evolution of primitive metabolisms a subtractive evolution is a conceivable alternative (Cairns-Smith and Walker, 1974). In such an evolutionary model it can be imagined that nothing is left of the original chemistry in present day life. In the domain of enzymatic catalysis it would mean that the enzyme developed during evolution a reaction essentially new and chemically without precedent. The results from bioorganic chemistry until now justify the assumption of an additive evolution as far as the mechanisms of enzyme catalysis are concerned, although it must not be forgotten that the results have been obtained also on the grounds of this assumption.

In this vision bioorganic chemistry is a science that tries to parallel biochemical and organic chemical results. The cofactors (including metal ions) belong together with a number of substrates to the oldest elements of life and are even older than life as we now know it. This can explain the success of bioorganic chemists in designing models for the enzymes that use a coenzyme. The problems that arise with the application of these concepts to biotin are presented in the following article.

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*Received September 13, 1977; Revised January 31, 1978*