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Edited by
G F Oster, I L Silver, C A Tobias

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Irreversible Thermodynamics and the Origin of Life

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FOREWORD

Thermodynamics might be called the "science of the possible". It offers no mechanistic answers; rather, it plays the legislative role of circumscribing the Universe of Physically admissible phenomena, and banishing to Ultima Thule those propositions with the audacity to violate her laws.

Inviolate though nature seems to regard these laws, nevertheless, each scientific generation discovers new aspects of the physical world, and finds those once sacrosanct canons more and more flexible, more dependent on context, and subject to various interpretations, modifications and amendments.

The great weakness of thermodynamics is that it is fundamentally a black-box theory. That is, it addresses itself not to the inner workings of a given system, but only to those relationships that must hold between external measurements. But this shortcoming is also the secret of its enduring success as a mathematical model for the physical world. Regardless of the contents of the black box, the input-output relations are constrained by its laws.

In search for plausible mechanisms to explain prebiotic chemical evolution, classical thermodynamics has heretofore suffered from a deficiency of another sort. It is a static theory, capable of correlating only equilibrium experiments; the so-called quasi-static processes are nothing more than a parametrized set of equilibrium states. Chemical evolution, however leisurely it appears on a geologic scale, was a dynamic process whose capacity for self-organization must have been intrinsically tied up with dissipative processes proceeding at a finite rate.

Irreversible thermodynamics, as conceived by Onsager and developed by Meixner, Prigogine, Katchalsky and others, has sought to extend the thermodynamic formalism to include these irreversible rate processes. Successful as this new phenomenology has been in other fields, it has never fulfilled its promise of becoming a model for biological dynamics in the same way that classical thermodynamics has been for chemical equilibrium. The reason lies in the intrinsic nonlinearity of biochemical processes, which fall beyond the purview of conventional thermodynamics.

It was only natural, therefore, that workers interested in the problem of chemical evolution should ultimately turn their attention to more powerful generalizations of thermodynamic theory in their search for theoretical insights into the origins of biological organization.

While the task of constructing the appropriate theoretical tools is still in its infancy, there have already emerged some important insights

FOREWORD

and a few tentative generalizations. Freed from the tyranny of linearity, new and surprising phenomena emerge which are extremely suggestive in biological terms.

The symposium in this volume brought together five noted scientists who have thought deeply on the problems of chemical evolution and pre-biotic organization. As the lively evening discussion session indicated, there are still broad areas of disagreement and controversy. We hope that these proceedings will help capture some of the excitement and stimulation felt by all those who attended.

The symposium took place at the Third International Biophysics Congress in Boston under the joint auspices of the international Union of Pure and Applied Biophysics and the Committee on Space Research (COSPAR). Thanks are also due to Orr Reynolds and the Space Bioscience Branch of the National Aeronautics and Space Administration for their interest and sponsorship.

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*"We deeply regret that, on July 4, 1972, one of the co-authors, Dr. Ira L. Silver, was killed in a traffic accident."

INTRODUCTORY REMARKS TO THE SYMPOSIUM ON THERMODYNAMICS AND THE ORIGIN OF LIFE

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The search for the origin of life is a direct conclusion of the theory of evolution. Since the Kantian recognition that the time of natural phenomena is measurable in millions of years, there is no escape from the attempt to reconstruct the pathway of the transition from inanimate matter to higher forms of organized life.

Kant stated already in 1755 in his "Nature and Theory of Heavens" that:

"Creation is not the work of a moment. Millions of centuries will flow on, during which always new worlds will be created, one after the other, in the distant regions. The creation is never complete."

In a world of this time scale it is unavoidable to follow the lead of Tyndall (1871):

"The human imagination would infallibly look behind the germ and however hopeless the attempt we would inquire into the history of its genesis. A desire immediately arises to connect the present life of our planet with its past."

It is in this light that we reconsider the belief of earlier centuries in a spontaneous generation. There is little doubt that it is not the ignorance and narrow mindedness of Plato and Aristotle, of Newton and van Helmont, of Harvey and Descartes, which led them to believe in inanimate origins, but the search for a unified picture of the world.

From a certain point of view the theory passed a dialectic cycle starting with the *thesis* - the belief in spontaneous generation - followed by the *antithesis* - which negated any inanimate origins, based on the work of Francesco Redi, of Spallanzani, and culminating in the brilliant studies of Pasteur - and finally leading to the modern *synthesis* initiated by Oparin and Haldane.

Although the synthesis resembles formally the thesis, it adsorbed all the knowledge and the scepticism of the antithesis. Thus it is evident that in the present day world no generation is probable and the evolution of life had to start in a non-Darwinian state, in a period preceding natural selection operating in organized systems: This was

realized by Darwin himself, who wrote to a friend:

"But if (and, oh, what a big if!) we could conceive in some little warm pond, with all sorts of ammonia and phosphoric salts, light, heat electricity etc., a protein substance was created, capable of experiencing further and more complex transformations - then at present time such a substance would have to be consumed or absorbed; which could not happen in the period preceding the formation of living creatures."

Darwin was therefore aware that a *physico-chemical evolution* preceded the biological and it is this evolution which may escape the criticism of the antithesis. It is the discussion of the forces and processes operating during the chemical evolution which is the object of this Symposium.

There is always a difficulty to indulge in a scientific analysis of the past. While the strength of physical science lies in prediction, it is weak in postdiction and reconstruction of historical events. Thus, given initial and boundary conditions, the equations of motion suffice for the prophetic prediction of all the future of macroscopic systems. In contradistinction to our personal experience, in which it is the past which is known and the future unpredictable, physical sciences have a great difficulty to reconstruct the irreversible path of previous events.

The only method open to us is the study of historical evidence of memory records, their arrangement in a consistent, logical system, and the experimental verification of possible mechanisms. Hence the experimental testing of different models becomes an integral part of the historical-evolutionary analysis.

The earliest event of importance for the physico-chemical evolution is the formation of the elements which according to a recent review by Unsold (*Science*, 1969) "the age of the Universe cannot exceed that of the heavy elements and therefore is limited to about seven billion years."

The earth in the present composition is about 4.5×10^9 years old and the reducing atmosphere in which chemical evolution presumably took place is between $3.5-2 \times 10^9$ years. The oxygen rich atmosphere, which coincides with the activity of living beings is about one billion years old. It is clear that the formation of the monomeric units of living systems was based on relatively simple molecules, of a monomeric nature, although recently Mathews and Moser made the suggestion that peptide synthesis preceded that of amino acids. The basic requirement is energy input to activate the rather stable elements and to induce combination to organic compounds. As is well known, the basic source of energy is UV radiation which at a wave length of 2000 Å provides 5-10 Kcal/cm²-annum and whose contribution was presumably higher before the development of the zone belt surrounding the globe. This energy suffices for the formation of a wealth of monomers from the available simple molecules (H₂O, CO, CO₂, CH₄, H₂, NH₃, HCN, dicyandiamide, simple acids and aldehydes). Indeed as early as 1913 Jacques Loeb synthesized glycine by passing an electric spark through a mixture of CO, NH₃ and H₂O.

Modern research of monomer formation was initiated by Melvin Calvin who obtained in 1951 formaldehyde and formic acid by irradiating water and CO₂. A rather dramatic breakthrough is the work of Stanley Miller in Urey's laboratory who obtained in 1953 a mixture of amino acids from a synthetic atmosphere of methane, ammonia, water and hydrogen.

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At present practically all the monomers of the important biocolloids have been obtained.

In a rather extensive thermodynamic analysis Dayhoff, Lipincott and Eck calculated the equilibrium constants for the formation of different monomeric compounds composed of COHN. The data are interesting as boundary magnitudes, there is, however, some doubt to which extent are equilibrium considerations applicable to the continuous process of chemical evolution in which monomers were converted into polymers and these proceeded to evolve into higher forms of organization. Although equilibrium thermodynamics is the reference base line for any further calculation, the non-equilibrium studies in both the linear and non-linear range may be found to be of more general interest.

This is particularly true when approaching the field of biopolymer development. As pointed out by Dixon and Webb (*Enzymes*, 1964), the conceptual difficulty of an information-rich polymerization seems at the present moment to be insurmountable:

"It has been pointed out - they say - that if the association of amino acids into a polymer were a completely random phenomenon there would not be enough mass in the Earth - assuming it were exclusively amino acids - to make one molecule of every possible combination of units in a low molecular protein."

Thus although a wealth of interesting studies on biopolymer formation are found in the literature, the field is open to further investigation on the nature of the physical forces which lead to organization and selection, to specificity and informational enrichment. Even if convincing mechanisms will be adduced for polymer formation the major problems of the chemical evolution of enzymatic activity and template reproduction of biopolymers will remain a major challenge for further study. It is important to note that with the establishment of more fixed structures endowed with the capacity of self reproduction natural selection becomes operative.

The major objective of this Symposium is the consideration of additional new physical factors which were not taken into account by previous workers. In the attempt to discover the physical foundations of the development of living structures it is up to the biophysicist to search constantly for additional and non-conventional processes which might have played a predominant role in the primary morphogenetic processes. It is of interest that recent developments in thermodynamics led to some intriguing conclusions on the possibility of obtaining structuring in time and in space, through the coupling of flows in a region far from equilibrium. These dynamic patterns seem to be related to certain organizational aspects of biology and deserve to be considered in an open biophysical discussion, devoted to the general consideration on *Thermodynamics and the Origin of Life*.

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CHEMICO DIFFUSIONAL COUPLING IN HETEROGENEOUS PEPTIDE SYNTHESIS

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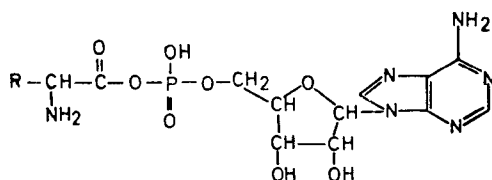
1. INTRODUCTION

The attempts to construct plausible models for the primeval synthesis of high polypeptides has led to some interesting procedures which deserve mentioning in this introduction. Since the primary step in the process is a condensation-dehydration, it was only natural to start in the anhydrous conditions which allow amino acids to combine into long chains. Well known are the experiments of Sidney Fox who found that by using glutamic, aspartic, or basic amino acids as starters it is possible to obtain a thermal polymerization to polypeptides of molecular weight 3000-10,000. The "protenoids" thus obtained give micro spheres endowed with some catalytic activity. G. Schram observed that the activation with anhydrous forms of orthophosphate leads to the formation of poly amino acids, polysaccharides and polynucleotides. (At 55° - 60°C, most efficient was a mixture of 10% cyclo-ethyl-metaphosphate and 30% linear ethyl-polyphosphates.) Using ethyl esters of polyphosphoric acids Young et al. obtained polyamino acids with microspherical protenoid structure as low as 25°C.

Gary Steinman, in Calvin's lab, looked into the possibility of anhydridisation in aqueous media. As a starting point he took the celebrated method of Khorana and substituted for the cyclodiimide with the dicyandiamide which could be produced from the primitive atmosphere. Indeed some polymerisation was obtained in acid solution according to the following reaction mechanism. Both polymerisation and copolymerisation rates were determined.

The interest in the process is in the introduction of an activated form of an amino acid, (A), which is capable of propagating a chain of polycondensation. The process, however, leaves open other problems, as discussed by J.D. Bernal in his famous lecture on the Physical Basis of Life in 1943:

"The primary difficulty of imagining the process going so far is, however, the extreme dilution of the system, if it is supposed to take place in the free ocean. The concentration of the products is an absolute necessity for any further evolution..



Amino acid—adenylate

Fig. 1

resonance stabilization energy among the purines and pyrimidines.

Further work of Ponamperuma showed that ATP may be formed by the re-fluxing for 4-6 hours of adenosine with a Graham salt. It is noteworthy that, while polyphosphates gave ATP, pyrophosphate was inactive in the reaction. Finally the interaction of ATP with amino acids leads readily to adenylates.

2.2. Upon dissolving adenylates in water at pH's slightly more alkaline than 7, they polymerize readily to oligopeptides of a DP ranging from one to eight. The study of my colleague Dr. M. Paecht-Horowitz, and her coworkers, led to the conclusion that the most plausible mechanism of the polycondensation is based on hydrolysis of the monomer (denoted as AP) with subsequent interaction of the adenylate with free amino acid or peptide.

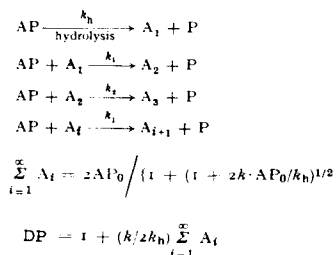


Fig. 2

and $d\text{A}_i/dt = k_{i-1} \cdot \text{AP} \cdot \text{A}_{i-1} - k_i \cdot \text{AP} \cdot \text{A}_i = 0$ at steady state. Assuming that all the polymerization constants are equal - an assumption valid in the range of alkaline pH's - the average degree of polymerization is:

$$\bar{P} = 1 + (k/2k_h) \sum_{i=1}^{\infty} \text{A}_i$$

where

$$\sum_{i=1}^{\infty} \text{A}_i(\infty) = 2\text{AP}_0 / [1 + (1 + 2k \cdot \text{AP}_0/k_h)^{1/2}]$$

A more sophisticated mathematical treatment carried out with Dr. Ailam allows the evaluation of the single rate constants.*

A typical run of polymerization is given in Fig. 3 where the concentration of each polymer is represented as a function of time, for the polycondensation of proline adenylate under constant monomer concentration. It will be observed that each polymer reaches a steady state; the time of relaxation increasing with the degree of polymerization.

It was found that the rate constants increase with pH and with the peptide chain length. The natural explanation is that polycondensation takes place through the interaction of phosphoanhydride groups with the free amino groups. Figure 4 represents therefore the ionization process $\text{NH}_2 + \text{NH}_2 + \text{N}^+$ and since the ionization constant increases with the peptide DP, so will also the apparent rate constants increase with the chain length.

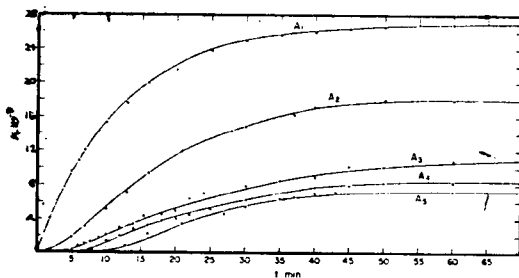


Fig. 3

2.3. Despite the interest in the homogeneous polycondensation, the low molecular weights obtained (see Fig. 5), make it highly doubtful that the peptides thus obtained could be regarded as precursors of primeval protein synthesis.

Thus it was useful to look for heterogeneous catalysts, of the Bernal type which might provide higher polymers - closer to the biopolymers of living systems.

3. POLYCONDENSATION ON MONTMORILLONITE

3.1. A preliminary staining of different clays showed that a clear-cut effect on the rate of polycondensation could be obtained only with the montmorillonite group. The montmorillonites are swelling clays,

*Note the competition of hydrolysis and polymerization when $k_h \gg k$

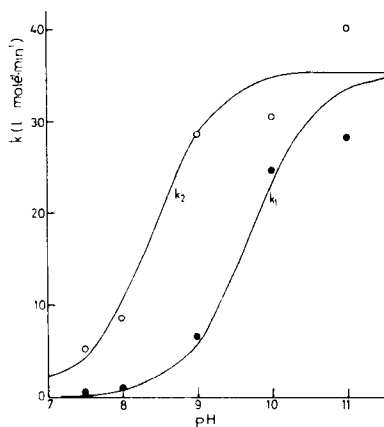


Fig. 4. pH dependence of the polymerization constants of alanyl adenylate. The curves are calculated and the points are experimental.

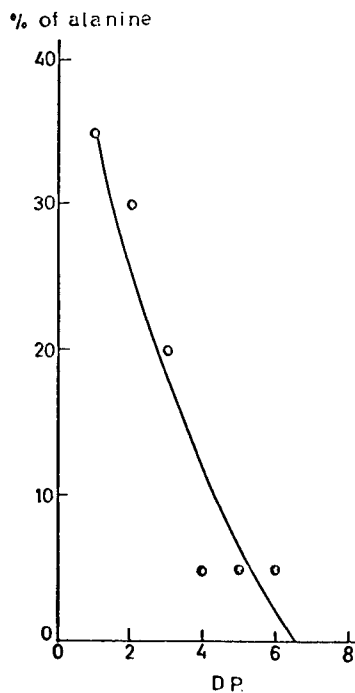


Fig. 5. Distribution of the molecular weights of polyalanines, obtained when alanine-adenylate is introduced into an aqueous solution at pH 8.5.

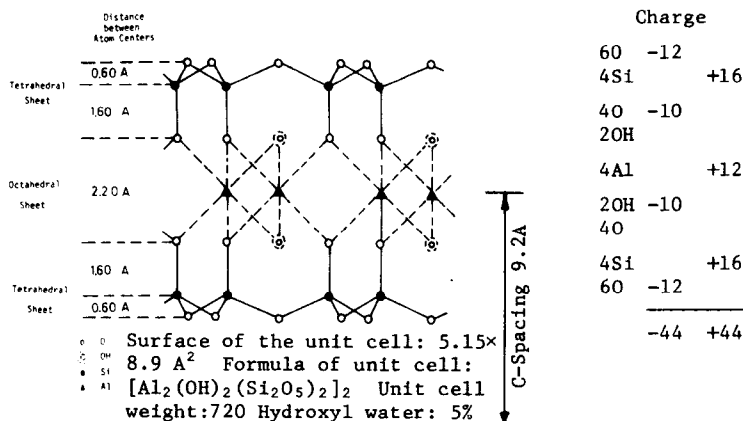


Fig. 6. Atom arrangement in the unit cell of a three-layer mineral (schematic).

which at high dilution, separate into single platelets whose structure is that of a triple layer depicted in Fig. 6.

Previous studies by colloid and soil chemists showed that adenylic acid as well as denine or adenosine do not adsorb on montmorillonite at pH 7-8 and room temperature. Amino acids are adsorbed at lower pH values but their adsorption is negligible in the pH range of biological systems. It was, however, remarkable that alanine and other amino acid adenylates are adsorbed strongly as shown in Fig. 7.

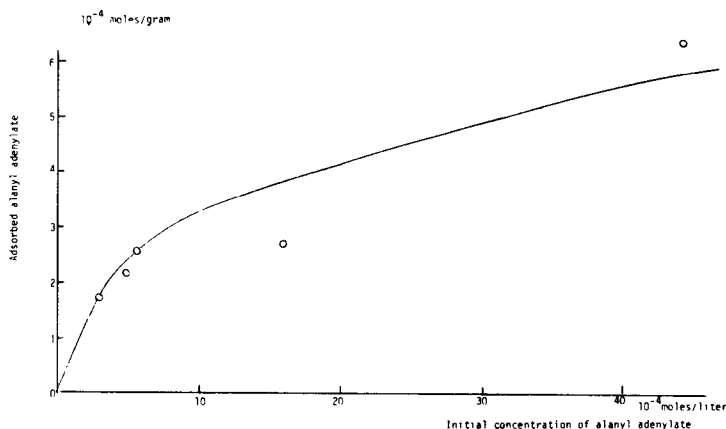


Fig. 7. Dependence of quantity of adsorbed adenylic acid on the initial concentration of alanine adenylate.

There is some difficulty in determining the equilibrium adsorption properties since polymerization starts immediately with the formation of high polypeptides. Indeed, as predicted intuitively by Bernal, the adenylates are protected by the montmorillonite against the hydrolytic processes

which compete effectively with the polycondensation, and hence in a few minutes polypeptides of over twenty amino acids are obtainable under physiological conditions.

Since the hydrolytic process is of minor importance on the surface of the heterogeneous catalyst, the scheme of polycondensation now may be represented according to the following scheme:

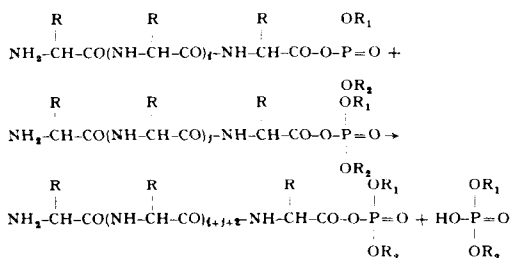
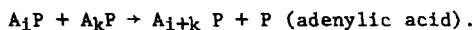
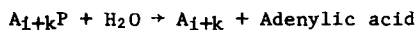


Fig. 8

which allows for rapid formation of high polymers according to the equation:



with the hydrolytic liberation of free peptides in the homogeneous phase.



3.2. The most intriguing aspect of the polycondensation is the distribution of molecular weights in the resultant polypeptides. It is well known that the separation of peptides in the range of ten to twenty mers is very difficult so that the results have to be regarded only as preliminary data. There is however a clear indication that the spectrum of molecular weights is discontinuous. Figure 9 shows the fraction of total amino acid in various ranges of molecular weights. It is observed that a small percent is now found in the range of molecular weights up to tetra peptides and then sharp and discrete peaks appear among decamers, eighteen and twenty-two mers. These peculiar results resemble closely the findings of chemico diffusional studies which predict a dissipative structure. Only in the present case, the dissipative structure is fixed in the polymeric chain length. A theoretical analysis of this interesting phenomenon requires a more careful consideration of thermodynamic coupling which leads to structure through the interaction of the polymerization process with the diffusion towards and from the catalyst particles.

4. REMARKS ON THE COUPLING OF REACTION AND DIFFUSION

4.1. The polycondensation reaction takes place in a well-stirred solution in which the diffusion coefficient may be assumed to be infinite. The montmorillonite particles are surrounded, however, by a stationary layer of several μ thickness into which monomers have to diffuse, and from which the reaction products have to diffuse out. During the last thirty years numerous studies dealt with the joint effect of the reaction and diffusional processes, and several criteria have been suggested

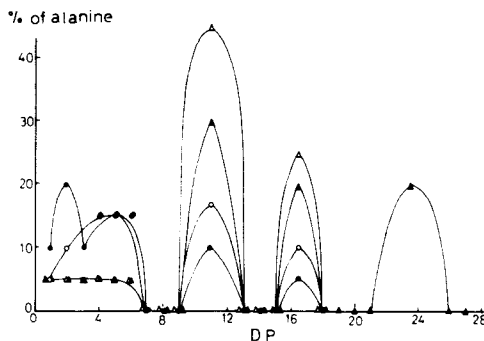


Fig. 9. Distribution of the molecular weights of polyalanines obtained when alanine-adenylate is introduced into an aqueous solution at pH 8.5, in the presence of various amounts of montmorillonite (mg/l): ●20, ○80, △220, ▲480.

concerning the contribution of diffusion to the overall reaction rate. In general, simple models were treated which are not suitable for more complicated cases such as a polycondensation process. It can be shown, however, that the thermodynamics of irreversible processes allows for a general treatment for reactions of any order and for coupling between diffusional flows, diffusion and reaction, as well as between chemical flows.

Consider an n component system undergoing n diffusional flows J_i ($i = 1 \dots n$) driven by local forces $\nabla(-\mu_i)$ where μ_i is the chemical potential of the i 'th component. The components may undergo a chemical reaction J_r driven by the affinity $A = -\sum v_i \mu_i$ where the v_i 's are stoichiometric coefficients - $v_i \equiv 0$ for the components which do not participate in the reaction. The phenomenological equations for the system are

$$\nabla(-\mu_i) = \sum r_{ik} J_k \quad (1)$$

$$A = r_R J_r,$$

where the r_{ii} 's and r_R are straight coefficients, the r_{ik} 's are coupling coefficients for diffusional flows.

In addition to the phenomenological equations we have to consider the equation of continuity

$$\frac{\partial C_k}{\partial t} = -\nabla \cdot J_k + v_k J_r, \quad (2)$$

which for steady states ($\partial C_k / \partial t = 0$) reduces to

$$\nabla \cdot J_k = v_k J_r. \quad (3)$$

From eq. (1) we obtain

$$\sum v_i \nabla(-\mu_i) = \nabla A = \sum v_i r_{ik} J_k, \quad (4)$$

while the application of the ∇ operator to eq. (4), and assuming r_R to be position independent, gives, with the aid of eq. (3)