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Chemistry and the Missing Era of Evolution

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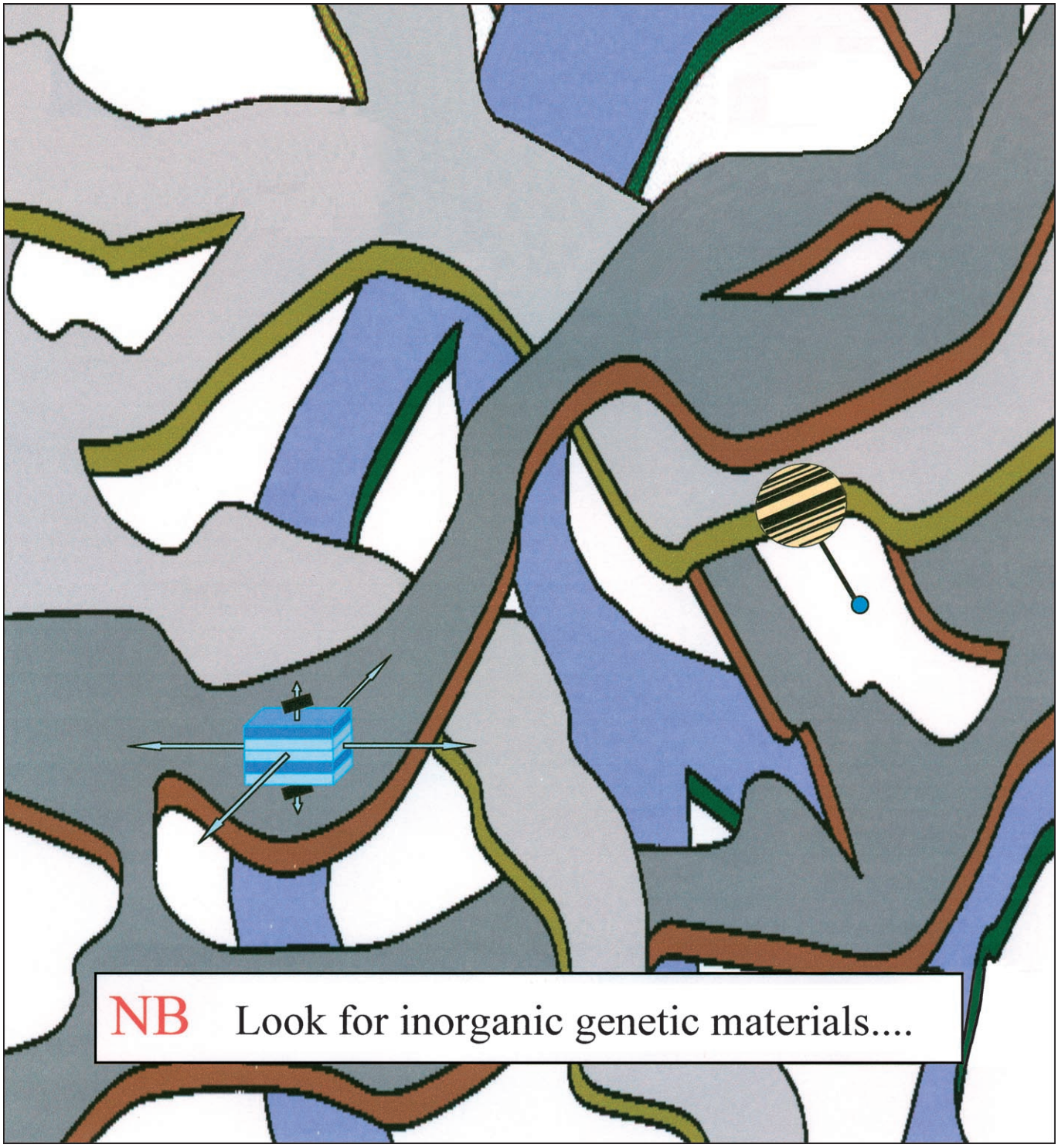

Abstract: The Darwinian evolution of life on earth depends utterly on complex molecular machinery, which, it seems, could only have arisen through a Darwinian evolution. The "RNA world" idea reduces this paradox, but requires a geochemically implausible supply of RNA monomers. A pre-RNA era of natural selection is implied. I suggest that originally this was based on inorganic materials that came to replicate permutations with specific (e.g. catalytic) effects.

Keywords: chemical biology · crystal growth · directed evolution · enzymes · inorganic chemistry

Introduction

"'*Holmes', I cried, 'this is impossible.' 'Admirable!' he said. 'A most illuminating remark. It is impossible as I state it, and therefore I must in some respect have stated it wrong.' "* (Arthur Conan Doyle: *The Adventure of the Priory School*)

Darwinian evolution is a kind of natural engineer that has given rise to the seemingly purpose-built features of the living things that we see all around us.[1] So it is reasonable to formulate the problem of the origin of life in terms of the origin of this creative force, and to try to imagine simple systems that might have been able to evolve through natural selection on the primitive earth. But let us not assume, as is so often done, that the kinds of materials on which evolution depends today would have been involved from the outset.

The opening question should not be: "How might the molecules of life have appeared on the primitive earth so that a Darwinian evolution could get under way?" The question is rather: "How might a Darwinian evolution have started most easily, based on whatever substances were appropriate and available?" Of course this is more cagey, but so it should be.[2] If we insist that we know what we don't really know, that the substances needed at the origins of evolution must have been similar to those that are now so essential, then we will, I think, have "stated it wrong", and made the problem impossible.

Part of the trouble here is with this term "the molecules of life". Yes, there is a set of molecules that can be said to be the building blocks of life as we see it now on earth. These are present in every organism we know of. Indeed our central biochemical control system with its DNA genes, protein enzymes, and so forth, is broadly universal too in its way of working. However, this system seems much too sophisticated, too high-tech (its parts too elaborately interdependent) to be anything other than a product of nature's engineer. If this is so, we should be thinking in terms of an earlier era of Darwinian evolution during which the essentials of our system were invented, and through which our current "molecules of life" acquired their significance.

In any case we can see the root cause of the present unity of central biochemistry as arising from (two) features of evolution, which are well understood,[3] rather than being a reflection of initial conditions. Firstly, we can see the central control system of life on earth as having descended from a "last common ancestor": some remote but highly evolved system possessing those general biochemical features that are common to all known life. Secondly, we can see that at the time of the common ancestor, this system must already have been fixed in its essentials, probably through a critical interdependence of subsystems. (Roughly speaking in a domain in which everything has come to depend on everything else nothing can be easily changed, and our central biochemistry is very much like that.[4])

The RNA world idea: The biochemical features that are common to all life on earth give us a view of the central molecular machinery of that "last common ancestor". We can even see a little way further back, to the later stages of the creation of our DNA/RNA/protein system.

By the late 1960s there were some who realised that RNA on its own might form the basis of a more primitive evolvable system,[5] because it has the formal properties needed: it can hold replicable information favouring its own propagation; or, in biological language, RNA can be both genotype and phenotype.

RNA, is structurally similar to DNA, but it is also formally like protein in that a strand of RNA can fold up on itself in a way that is largely determined by the particular sequence it contains. By the 1970s there were suggestions that enzymes used to be made of RNA.[6] This speculation was given a boost in the early 1980s when it was shown that not only might RNA molecules have acted as catalysts in the remote past, but they still do![7] RNA enzymes, or "ribozymes" as they are called, have been found to be part of the standard machinery of cells. Then in 1986 the term "the RNA world" was coined,[8] to refer to the idea that a purely RNA genetic-control system preceded our present DNA/RNA/protein system. Further confirmation of this comes from the more recent discovery that the main working parts of ribosomes (the huge nanomachines that stitch together amino acids to make proteins) are essentially made of RNA with associated proteins in more peripheral roles.[9]

Directed evolution: A line of research, which started in the 1960s,[10] has demonstrated that RNA molecules (and now also DNA) can be made to evolve in the laboratory and this has since led to a completely new way of doing chemistry, described as directed evolution.[11] It is a way of producing

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RNA molecules that have highly specific properties, as ligands or catalysts for example.[12]

Side stepping the technical details, here would be a typical approach to producing RNA molecules that could bind specifically to a particular small molecule X. Start with a collection of RNA molecules each containing a random sequence, say 25 units long. As there are four kinds of units in the RNA co-polymer a particular sequence of them would be one of 4^{25} ($\approx 10^{15}$) possibilities. (We can imagine most of these folding up to make different rather complicated three-dimensional structures with different arbitrary arrangements of little grooves and other features, each arrangement determined by its particular random sequence.) Then we should apply a selection procedure that would fish out those RNA molecules that just happen to have some affinity for molecule X—say, by using a column of material to which molecules of X have been attached.

Perhaps one in a hundred of the RNA sequences would turn out to be tolerable ligands for X. However, suppose we wanted a beaker-full of something a bit more special: say, a ligand that could distinguish X from the structurally similar X′, or was a specific and efficient catalyst for the reaction of X to Y, but what if the frequency of what we were looking for was not one in a hundred but one in a trillion (10^{12})?

It would be possible in principle to find such a rarity, because RNA molecules not only have sequence-dependent properties, their sequences can also be replicated ("amplified") indefinitely. For example we might imagine starting with a collection of RNA molecules, creaming off the best 1%, multiplying these a hundred fold, again selecting the best 1%. After six such cycles we would be at the one-in-a-trillion level of creaming! Well, there are provisos,[11] but a real experimental quest of this sort started with a pool of over 10^{15} RNA molecules with mainly different random sequences: "After a few cycles of selection and amplification, one can recover the descendents of a single functional molecule from the initial population."[13] Such a technique resembles natural evolution in that it too depends on a combination of selection and amplification. And it all helps to support the notion that RNA preceded protein in our evolutionary history. However, it does not say that RNA, or anything like it, was the very first genetic material.[4,14]

The Evolution of Organic-Chemical Competence

What is missing from this story of the evolution of life on earth is the original means of producing such sophisticated materials as RNA. The main problem is that the replication of RNA depends on a clean supply of rather complicated monomers—activated nucleotides (Figure 1).[14,15]

What was required to set the scene for an RNA world was a highly competent, long-term means of production of at least two nucleotides. It has been known for a long time that some nucleotide components can be formed under relatively simple conditions, most famously sugars from formaldehyde and adenine from cyanide. (More recent ideas would have borate to stabilise ribose, and formamide in place of cyanide.[16]) A recent geochemical suggestion is that nucleotide components might have been formed and stabilised under alkaline conditions of low-temperature hydrothermal fluids.[17] In practice the discrimination required to make nucleotide parts cleanly, or to assemble them correctly, still seems insufficient.

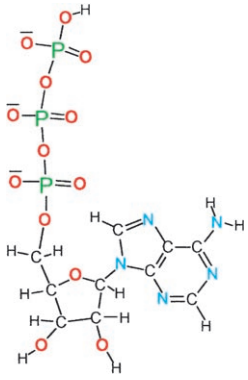


Figure 1. How the 44 atoms in ATP are connected. This is one of the four activated monomers required today for RNA replication.

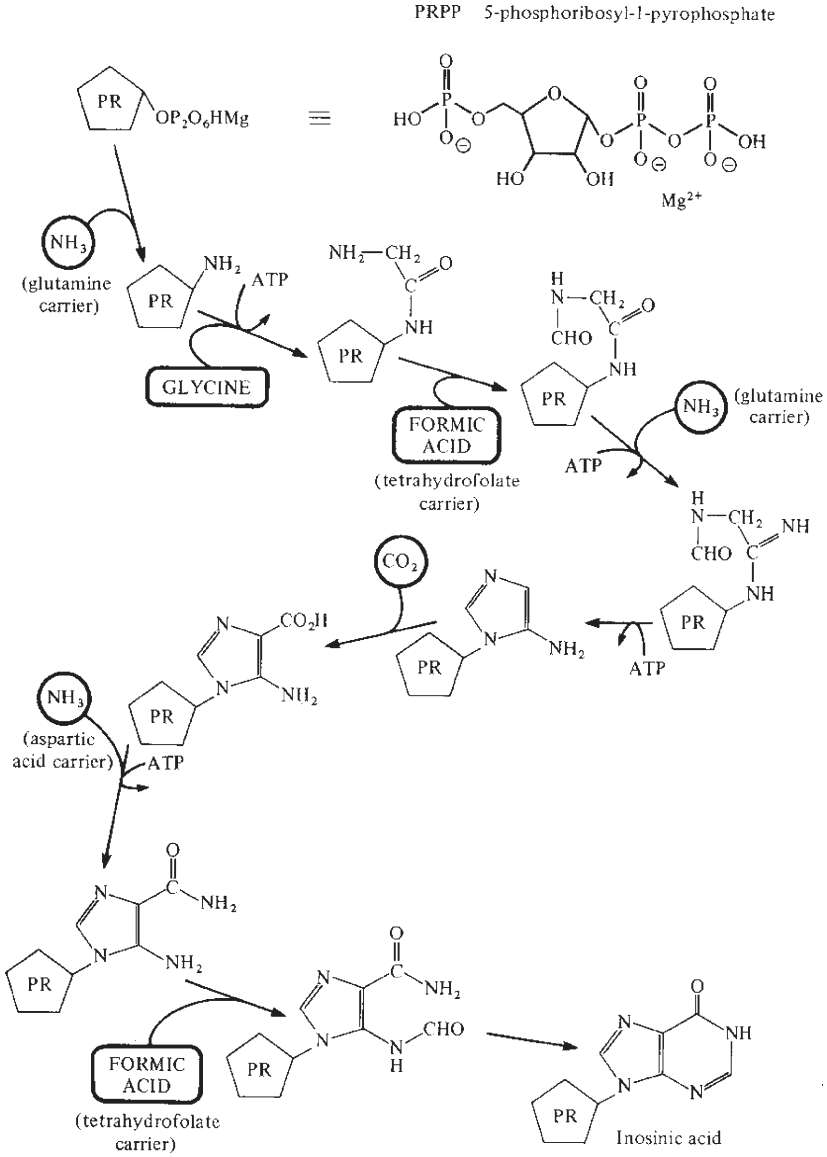
Some indication of the depth of this problem is seen in the present metabolic pathway for making purine nucleotides. Scheme 1 is a simplified picture that refrains from detailing the structures of the enzymes, the high-energy co-enzyme reagents, group carriers and so forth on which such syntheses depend (and on which life on earth *now* depends). There is little room for incompetence here. Loose control would certainly lead to side reactions, often to products that were similar to, but not quite the same as, the required nucleotides. Such molecules are particularly liable to jam the works—they are called "antimetabolites".

It is a reasonable guess in our present state of knowledge that only nature's engineer, evolution through natural selection, could have achieved the required level of organic-chemical competence for an RNA world to become possible: implying a missing era of evolution based on altogether simpler genetic materials.

Genetic takeover: The details of the real story are still beyond our reach, but Figure 2 illustrates in its simplest form a general common sense mechanism for radically changing genetic materials. "Common sense" because it is like the way in which new technologies displace old ones in our society.

Primitive and advanced mechanisms for comparable functions seldom use the same stuff. Think of quill pens and word processors, or horses and motor cars. Typically one thing does not convert to the other, rather there is a (gradual) takeover. Likewise a genetic takeover would not require that a secondary genetic material should be structurally similar to the primary one, or that any information need pass between them. Indeed I think that organic molecules, so excellent for highly evolved life forms, are simply not suited for truly primitive genetic materials or catalysts.[4,20–22]

Enlarging on Figure 2, an early takeover might have worked something like this. The first genetic material G1 is some inorganic mineral that holds its information as permutations of microcrystalline irregularities that 1) replicate through crystal growth and 2) affect structural, adsorptive, catalytic or other such properties of the material that holds them: properties that in turn affect the chances of survival,



Scheme 1. Part of the current synthetic pathway to purine nucleotides (there are four more steps to ATP).[18]

replication or propagation of the genetic material in given surroundings. As part of this, organic molecules in the surroundings are being adsorbed and altered to generate, at first, crude mixtures within distinct phenotypes. Such local entrained organic "soups" are useful for unsophisticated functions: as glue perhaps, or gel-forming agents, or pH buffers. Crude synthetic ability is then refined through improved catalytic specificity of the genetic material so that eventually clean supplies of particular molecules are produced, and well-organised organic polymers become possible for the first time that are used for more sophisticated phenotypic functions.

Eventually, in some lines of descent RNA-like molecules, including perhaps simpler versions of our RNA,[23] have found some phenotypic use providing selection pressures to refine the production lines to these materials.

Hence the scene would be set for, well, not an RNA *world* exactly, more a suburb. For according to this takeover story, there would have been a long period during which G1 and G2 would have been operating together in a kind of symbiosis, with G2 utterly dependent on G1 to begin with for the provision of nucleotides. It would only have been much later that the earlier genetic material, G1, could finally have been disposed of.[4]

A Design for a Primitive Gene

We start from home, as it were, with the familiar picture of the DNA molecule in mind. We can see it as a stack of little plates ("base-pairs") held in place by two entwining sugar–phosphate strings forming a

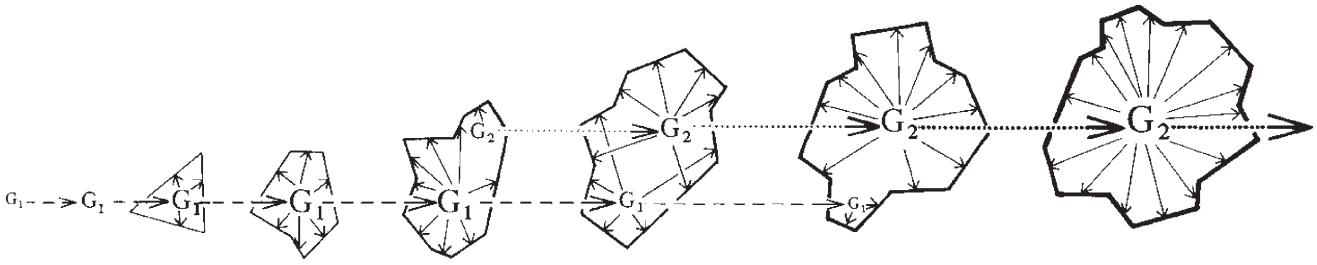


Figure 2. Formal representation of a genetic takeover.[19]

double helix. Now with the aid of toy brick models we will try to get to something simpler while maintaining the "informational" aspect of DNA.

Permutation—the key to information capacity: In Figure 3 (top) we have untwisted the helix to show in formal terms how the bases connect through a number of hydrogen bonding "plugs" and "sockets". We can see that at any position in the stack there can be either of two kinds of base-pairs in either of two orientations (Figure 3, bottom).

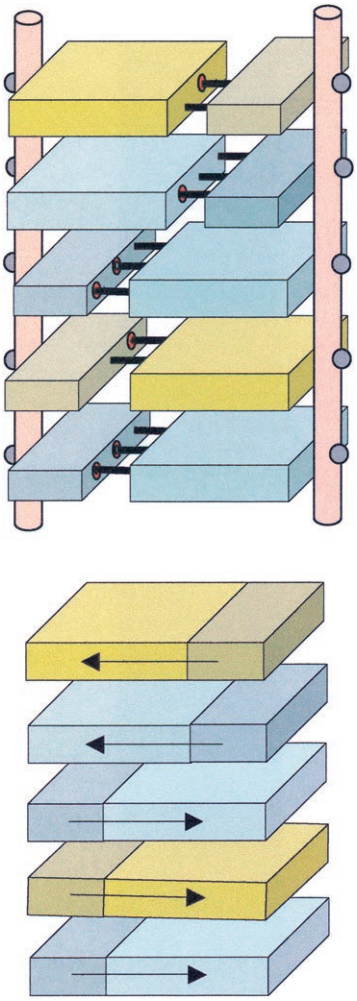


Figure 3. Top: Toy block model of DNA. Bottom: The two permutable features of DNA base-pairs: of kind and of orientation.

Thus even a very modestly sized stretch of a DNA molecule, a sequence of, say, 150 base pairs, holds a huge amount of information in the sense that it is one sequence out of an astronomical number of permutations: 4^{150} ($\approx 10^{80}$)—more than "the number of protons in the universe".[24]

Having "rubbed out" the sugar–phosphate strings responsible for preserving the sequence information in DNA we now do something even more shocking and do away with base-pairing, which is so much part of the replication mechanism for DNA. In place of pairs of bases that can connect and disconnect we substitute simple blocks or "unit layers" stacked on top of each other like cards in a pack (Figure 4).

We have preserved the most essential feature of DNA, its permutability, but these images can equally be seen as formal representations two kinds of layer crystal that are quite common especially in the mineral world.

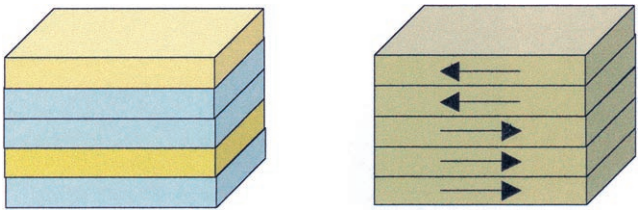


Figure 4. A permutation of chemically different layers (left) and of different orientations of chemically identical layers (right).

In cases in which the unit layers are of chemically different kinds (like Figure 4, left), they are called "mixed layer crystals"; those in which the layers are chemically the same, but stacked with different orientations, they are "polytypes" (Figure 4, right). Either kind may have a simple repeating sequence or, more interestingly for us, they may be disordered as shown.

A prominent difference between the stacking sequence in DNA and in the "crystal genes" we are trying to imagine is in the dimensions. Instead of DNA's long thin stack of tiny platelets we are imagining unit layers that are of similar thickness (about a nanometre), but as broad as you please in the other two dimensions (microns, millimeters or more.). No need then for strings to preserve a particular sequence. Instead the layers are held in place by ordinary interlayer forces.

This would be far less efficient as an information store than DNA. Yet even a stack of 100 or so unit layers of two different kinds could still have $\approx 10^{30}$ permutations.

Layer silicates, such as clay minerals, offer some promising models, especially since these readily interact with organic molecules in their surroundings.[25,26] A unit layer in these materials has a sub-layer or "octahedral sheet" approximating either to aluminium hydroxide (gibbsite) or magnesium hydroxide (brucite). Each of these kinds has a silicon–oxygen network, a "tetrahedral sheet" fused either on just one side of the octahedral sheet (the 1:1 class), or on both sides (the 2:1 class); for examples see Figures 5 and 8 (later). This gives four major categories within which there are further types, for example, according to the strength of the electric charge, if any, arising from cation substitutions within the unit layer. Thus the stacks in mica crystals consist of strongly negatively charged 2:1 layers firmly held together through nested intervening cations, typically potassium.

The unit layers of the asymmetric 1:1 classes generally have little if any charge, but have a dense array of hydroxyls on one of their flat surfaces and oxygen atoms on the other, so that here the layers stick together through hydrogen

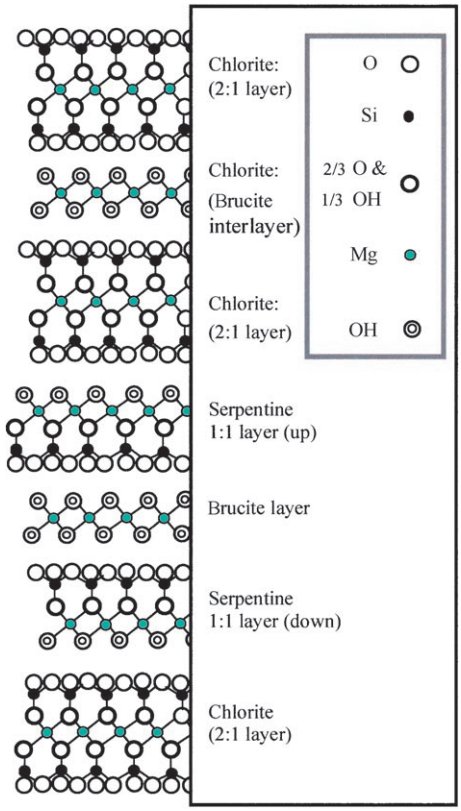


Figure 5. Idealised model of two of eight irregular interruptions by serpentine layers observed[27] in a chlorite stack.

bonding. The similar geometries of the major layer silicates results in mixed layer structures being quite common.[28]

Chlorite is a mixed-layer material, the idealised structure of which is a regular alternation of uncharged 2:1 layers and (much thinner) naked brucite layers that hold together through interlayer hydrogen bonds. However, real chlorite hardly ever conforms to this ideal: internal cation substitutions create charges in both the constituent layers tending to increase their mutual cohesion, and there are numerous slightly different stacking modes (polytypes), as well as more substantial mixed-layer irregularities. An example of the latter is shown in Figure 5.

Edge-only growth--the key to replication: A crystal stacking sequence could be amplified (reproducing vegetatively) if, during crystal growth, units were to add exclusively to the edges of the layer stack, so that its sequence is copied into newly forming crystal (Figure 6).[29]

The formation of the mica-like clay mineral illite in the form of ribbons of a remarkably even thinness,[30] strongly suggests formation through edge-only growth. Rectorite, is a minimal example (Figures 7 and 8).

It is not clear whether these ribbons grew as free-floating structures or originally as a stack of layers that subsequently peeled apart,[32] but either way they add to a strong impression that clay minerals grow by sideways accretion of dissolved units. Figure 8 is a side view of a model of a rectorite

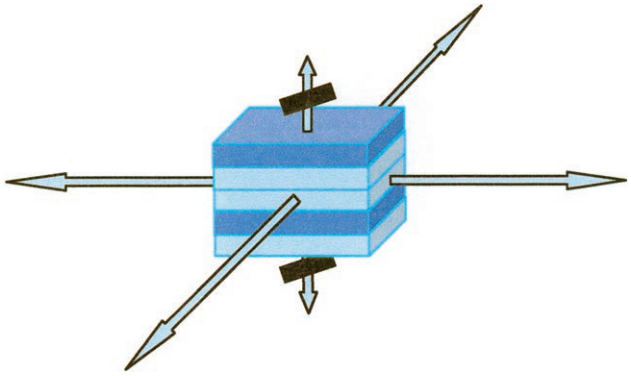


Figure 6. How to amplify sequence information through crystal growth.

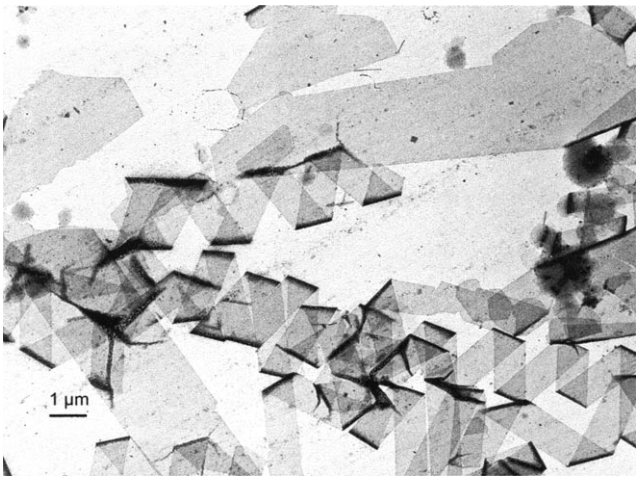


Figure 7. Transmission electron micrograph of rectorite.[31]

ribbon. A ribbon like this (or a stack of them) would probably have grown by edge accretion of small units such as silicic acid and hydrated cations. This would be a crystallisation, but also a polymerisation, because each addition of a silicic acid or hydrated cation unit requires the making and breaking of several bonds with the elimination of water. If they grew sub-layer on sub-layer, the partly formed unit layers would usually be unstable.[29]

Edge-only growth has been suggested as part of the explanation for the repetition of long irregular stacking sequences within domains of (mixed layer) barium ferrites.[33] It was supposed that an initial stack of layers, in some arbitrary irregular sequence, grows by the addition of atoms exclusively to the edges of the stack. The growth is uneven and branching, giving rise to an apparently disorganised overlapping mass of fronds ("like seaweed"). However, according to this model the growth is exclusively sideways so that each frond has the same sequence of layers.

Figure 9 (top) is an impression, based on this idea, of what a truly primitive gene might look like. The combination of branching and flexibility can lead to a high relative proportion of edges in which the characteristic sequence is displayed as a kind of "bar code" (Figure 9, middle).

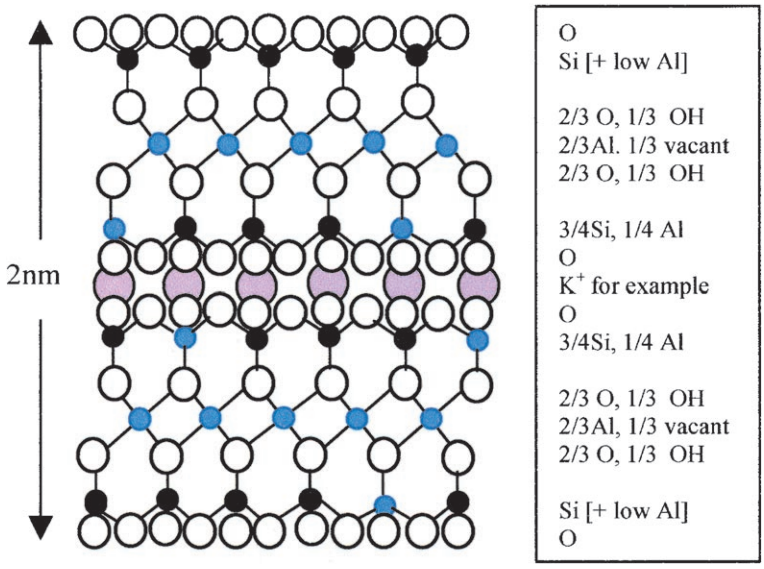


Figure 8. Typical rectorite structure with two mica-type unit layers. This (*y* axis) projection conceals the octahedral vacancies and OH groups listed on the right hand side.

As for its phenotype this could be slight, perhaps at first unnoticeable, reflecting some simple direct effect of the genetic information. For example, whether such a gene sticks appropriately to the grains in a sandstone,[4,20] or whether weaknesses tend to develop to facilitate pieces occasionally breaking off to establish a new colony elsewhere. Such things might depend on how wide the fronds are, how flexible, how rich their branching, how grooved their edges, and such things might indeed be influenced by stacking sequences.

For example, within the asymmetric 1:1 serpentine layer the hydroxide sub-layer is a little oversized to fit the silicate sheet exactly, so that these unit layers on their own tend to roll up, carpet-roll fashion, with the hydroxide sheet on the outside. There is bound to be some strain, then, when serpentine layers are flattened elements of a mixed layer structure such as shown in Figure 5. The effect of this would tend to be transmitted to adjacent layers above and below diminishing with distance.[34] This might show up as a tendency for a stack to curl or limit growth in certain directions and would in any case modulate the edge structure.

The origin of metabolism: A number of distinguished authors have regarded some kind of metabolism as having played a prior part in the origin of life, before the replication of information through genes of any kind.[25,35] I am of the other, "genes first", camp and take metabolism to mean chemical reactions *under genetic control*. It is indeed a critical feature of the primitive-crystal–gene concept that no sort of organic metabolism was needed at the very origins of our evolution. Like most of the characteristic features of life as we know it, metabolism was not, on this view, a prerequisite for evolution, but rather a product, albeit perhaps an early one.

A rough kind of metabolism might have started from incidental catalytic edge sites in the genetic material that could locally alter organic molecules in the surroundings to favour the propagation of the genetic material. (Dicarboxylic acids can favour layer silicate synthesis for example.[36])

Matters Arising

An embarrassment of riches? Indeed there may well have been no shortage of genetic materials on the primitive earth. Even just among layer silicates there is a plethora of possibilities.[4,20] However, there are other permutable layer structures too; for example, double hydroxides have recently been suggested as primitive information stores.[37] Indeed polytypism and mixed layering are possible in materials that are not intrinsically layer materials at all.[27] Planer intergrowths of different members of the ABC-6 group of zeolites provide an example of this kind of thing.[29,38]

If indeed there are numerous minerals that could act as primitive genetic materials this could change the way we think about the puzzle of the origin of life—from wondering how anything could have worked at all as a genetic material on the primitive earth, to wondering which of dozens of possibilities was the material in question—and then at the same time having to explain why we do not have life originating all the time, all over the place!

Well, "life" is not a well-defined term. As implied at the start of this piece it can be said to describe a sort of natural engineering that is a typical long-term *product* of natural selection. "Evolvable systems" is safer and describes what must have come first, and, yes, I think that tiny, trivial and temporary evolutions are indeed happening almost anywhere that crystals are growing, because crystal growth tends selectively to propagate imperfections that assist crystal growth.[39] The question is how and under what circumstances evolutionary processes might have gone beyond the tiny, the trivial and the temporary.

Consortia? Given so many possibilities for mineral genes, we might think about collaborations between different genetic materials. (In some ways like a bacterial consortium, in which different species of bacteria collaborate to produce a mutually beneficial effect,[40] except that in the bacterial case the underlying genetic information is all written in the same genetic material—DNA.) Perhaps one of the interleaving genes in my final cartoon (Figure 9, bottom) acts as

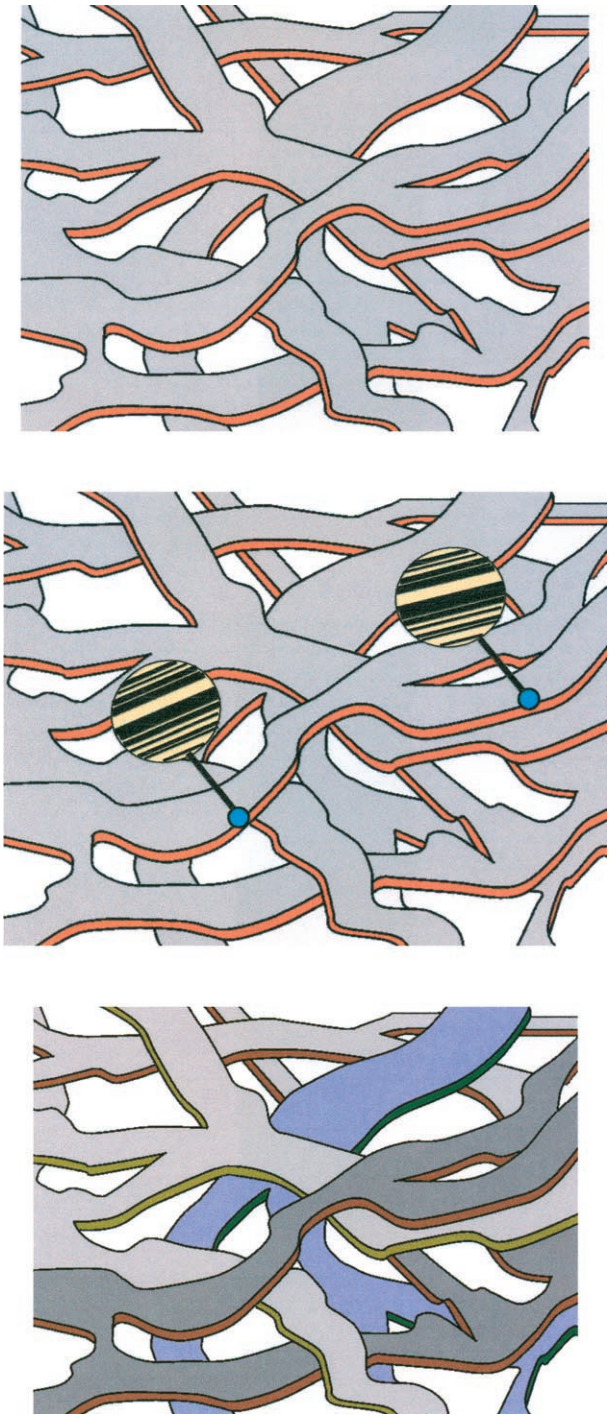


Figure 9. Top: Could an untidy looking thing like this be a primitive gene? Middle: Are the "bar codes" all the same or not? Bottom: Or is it a "consortium" of chemically different primitive genetic materials?

a pH buffer. Another has catalytic edge sites for making carboxylic acids to mobilise aluminium and hence catalyse layer silicate synthesis.[36] A third kind is perhaps "connective tissue" with an edge structure that sticks to the surrounding rock and loosely self associates to make a gel, so that between them they produce a local environment—a communal phenotype—conducive to their mutual survival and replicative growth.

Multiple overlapping takeovers? Returning to the genetic takeover concept one might think of a richer and more continuous version of Figure 2 describing that era when our now fixed genetic system was being invented. It would be an image in which *many* genetic materials are being added and subtracted in different lines of descent,[20] and in response to particular selection pressures. Inorganic crystalline materials would have been the starters, according to our story, and would have remained predominant until a sufficient organic-chemical competence had evolved. However, I would guess that as organic genes were becoming possible there would have been a second phase of trial and error in a variety of niches, including perhaps some of the RNA-type molecules that have been proposed as precursors of RNA.[23]

Overall we might see the missing era of evolution as being characterised by evolving systems that had multiple genetic materials coming and going: the kind of flexible situation in which different designs could, as it were, be tried out.

Inorganic enzymes? Eventually there must have appeared those not-so-primitive evolving systems that would set the scene for RNA as a genetic material by establishing metabolic routes to complex molecules such as ATP in at least one line of descent (and originally for purely phenotypic functions). We might suppose that *enzymes* would have been needed for this, by which I mean well-tuned, evolved catalysts. Not proteins, of course, nor RNA to begin with, but evolved inorganic enzymes.

An immediate argument *for* such a conjecture is that most heterogeneous catalysts, such as are used in industry for example, are inorganic materials. An immediate argument *against* is that such catalysts are not usually very specific.

We must admit that protein and RNA enzymes are in a different league from other catalytic materials, but we should recall that these are "informed" molecules: which is to say that a particular enzyme, whether of protein or RNA, belongs to a relatively tiny subset of an astronomical number of permutations, a subset that was discoverable only because the molecule was subject to evolution through natural selection.

We have never seen an evolved (highly "informed") inorganic catalyst, so it is hard to judge how effective such a thing might be. We might well question whether such a thing could ever be specific enough to be called an enzyme. According to Pauling's theory a protein enzyme binds, and thus stabilises, the transition state of the reaction it catalyses; and it might seem that inorganic crystalline materials, however "informed", would simply not be flexible enough to create the kind of intricately defined "socket" needed for enzyme action.

On the other hand Pauling's theory of enzymatic catalysis is now quite widely regarded as insufficient, because it ig-

nores the thermal fluctuations that take place in a protein molecule on femto- to millisecond timescales. Protein dynamics are now at the front of thinking about enzyme action, as seen in a recent Royal Society discussion on the subject of "Quantum catalysis in enzymes: beyond the transition state theory paradigm".[41]

It now seems that an enzyme's control of a chemical reaction is more active, more *manipulative*, than just making a matching socket for a transition state. It seems that it is not so much a static socket that is matched to the reaction of a substrate, but a set of motions.[42,43] Evidently this includes global motions, because catalytic activity may sometimes be unexpectedly strongly influenced by amino acid residues distant from the substrate binding site. Dihydrofolate reductase, for example, is described as having "a network of coupled promoting motions that extends throughout the protein and involves motions on femtosecond to millisecond timescales".[44]

Now a crystal is no more a static object than is a protein molecule. Lattice vibrations are part of its being. So perhaps an irregular lattice in a multilayer crystal could produce similar effects to the "promoting motions" of protein enzymes: that the complicated way a bound substrate is pushed and pulled by local forces, that is, the way it is "manipulated", might depend on global aspects of the crystal's structure, on its particular irregularity, its sequence "information".

Of course this is a long-shot speculation. What actually happened in early evolution is likely in any case to have been complicated, perhaps involving the incorporation of more specifically catalytic materials, such as the ABC-6 zeolites referred to earlier, or with additional non-genetic inorganic structures, such as polyoxometalates, with their flexibility and nanostructure-forming propensity.[45]

There is a world of phenotypic possibilities here but to explore it we will need, first, to make (or find) robust replicators, perhaps of the kind illustrated in Figures 6 and 9 (middle).

Acknowledgement

I am grateful to the University of Glasgow for an Honorary Senior Research Fellowship in the Chemistry Department.

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