

Aspects of Nucleic Acid Structure and Function

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ABSTRACT

Despite decades of intense study, certain physico-chemical aspects of the nucleic acids—the genetic repository of life—remain enigmatic. Thus, solutions of DNA are apparently constituted of varying amounts of double and single-stranded forms, with melting studies being inconclusive about the effect of temperature on the composition. Consequently, this casts doubt on current estimates of the thermodynamic stability of the base pairs. However, the overwhelming stability of the Watson-Crick model is adumbrated by a kinetic analysis of the action of DNA polymerase, microscopic reversibility indicating that polymerase action is kinetically controlled, whereas proof reading-excision is thermodynamically controlled.

The structural basis for the differing roles played by DNA and RNA in the sustenance and propagation of life also remains to be clarified. It appears that formation of the RNA double helix is sterically inhibited by the 2' ribose hydroxyl group, which is also relatively inaccessible to external base, thus enhancing hydrolytic stability. The in vivo conformation of RNA is likely determined by the requirements of its appointed biological role, the large size of tRNAs being particularly significant in possibly leading to enhanced specificity in its interaction with the corresponding tRNA synthetase. The proclivity of RNA generally to remain single stranded may indeed be the reason for the existence of viruses as stable RNA-protein complexes.

The preeminent role of nucleic acids as “genetic guardians” is, however, blurred by the fact that the translation of the genetic code is contingent on the action of the various tRNA synthetases. This implies that the genetic code is manifested via codon-anticodon specificity only by the involvement of protein molecules that are unique to each codon-anticodon pair. This has intriguing implications

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for the origin and evolution of the genetic code, possibly indicating that the tRNA synthetases are a relic of prebiotic protein-nucleic acid hybrids (thus also raising doubts about the RNA world hypothesis).

Keywords: *Codon-anticodon; DNA; microscopic reversibility; nucleic acid melting; RNA; tRNA synthetase; virus; Watson-Crick.*

1. INTRODUCTION

1.1 Nucleic Acids — Life's Molecular Blueprint

Biological life is characterized by the propagation and sustenance of a plethora of species, often interconnected and interdependent, and continually driven by the consumption of energy. The orchestration of this web of infinite complexity—both intraspecies and interspecies—is masterminded by a molecular code of stunning simplicity and unerring consistency. This is essentially a code of inheritance, and although hindsight suggests its inevitability, its heroic unraveling was critical to transforming biology into a modern science based in the immutable laws of physics and chemistry [1-3].

The idea that inheritance employs its own currency—with the “gene” as its unit—was a key development in science as a whole. Indeed, the metamorphosis of the gene idea, from its early Mendelian roots to its modern molecular avatar, launched the era of molecular biology, which is central to the reductionist view of life. These developments were enabled by the discovery of the structure of DNA in the 1950's, undoubtedly one of the greatest scientific achievements of all time [4]. The subsequent discovery of RNA led to the recognition that the nucleic acids served as the repositories of the molecular code of life.

The succeeding decades were witness to the explosive development of molecular biology, aided by experimental studies of greatest ingenuity and theoretical insights of highest acumen. The resulting unraveling of the genetic blueprint of life meshed—unsurprisingly—with parallel developments in the evolving science of biochemistry, particularly pertaining to complex metabolic pathways as controlled and regulated by enzymes.

Key ideas constituting the current dogma of biology evolved thenceforth: in particular, the view that information flows in the direction DNA→RNA→protein, and the one gene—one

enzyme hypothesis. Thus, holistic biology now demands a physico-chemical explication of its characteristic phenomena, leading—tentatively and intriguingly—to the possibility that mind itself can be explained by the laws of matter!

1.2 Biology in Terms of Physics and Chemistry: Molecular Genetics

The above discussion leads to the view that life needs to be understood in terms of the laws of physics and chemistry, particularly those governing the behavior of molecules in all their forms and manifestations. The nucleic acids are the molecules that determine the laws of inheritance: Intriguingly, however, this statement is arguable, as it raises the sublime question whether nucleic acids were coopted to serve the larger interests of biological evolution, or whether biological evolution was—to whatever extent—contingent on the properties of nucleic acids!

What is inarguable, however, is the fact that a thorough understanding of the properties and reactions of nucleic acids—as molecules—is essential to the reductionist view of biology. Modern chemistry—aiming to attain the mathematical exactitude of physics—is the science that deals with molecular phenomena at the highest level of sophistication. Several of the theories of chemistry—particularly those dealing with the laws of kinetics and equilibrium—are based in the established laws of physics [5]. Thus, it would be enlightening to draw upon the theories of chemistry in our efforts to understand the behavior of the molecules of life, and biological phenomena in general.

In the following sections, certain aspects of the properties of nucleic acids are discussed, with the broad aim of reaching an understanding of these properties in relation to their biological significance. These include: the phenomenon of nucleic acid melting (key to understanding their stability in terms of base pairing); DNA biosynthesis and a kinetic analysis of the action of DNA polymerase; key structural aspects of RNA as concern its biological role; and certain

intriguing evolutionary implications of the tRNA synthetases.

A discussion of these aspects is opportune, not least because they are apparently beyond the pale of conventional treatments. However, only relevant physico-chemical aspects are considered herein, a background familiarity with the topics being also assumed.

2. DISCUSSION

2.1 Studies Related to DNA

2.1.1 The DNA double helix

Although the DNA double helix remains a sacrosanct principle of modern science, it is apparently not beyond question. A detailed critique of the double helix has been presented recently [6]. Thus, although the evidence for the double helix in the crystalline state is incontestable, the evidence is less clear-cut in the case of the solution state. In fact, there is fairly convincing evidence for the existence of varying extents of the single stranded form in the solution state, as revealed by concentration effects on the UV absorbance, indicating an equilibrium between the double and single stranded forms.

Intriguingly, however, the thermal separation of the complementary strands on the double helix is apparently forbidden by high thermodynamic barriers, because of the additivity of the base pairing strengths. These and other considerations are discussed in more detail in the following section on nucleic acid melting, an intriguing technique that has been frequently employed for estimating the stability of the double helix.

It is also noteworthy that the stability of the duplex form in the crystalline state indicates that the compact and symmetrical shape of the duplex would also be preferred in the confined *in vivo* environment of the chromosomes. Perhaps these conditions may be simulated *in vitro* under high pressure also, indicating an avenue for further studies.

2.1.2 Nucleic acid melting

Nucleic acid melting involves heating a solution of a nucleic acid, usually DNA, and following the changes in the ultraviolet absorption band at ~ 260 nm (Fig. 1a) [7,8]. It has been generally believed that the observed changes serve as

evidence for the gradual unwinding of the double helix of the DNA molecule, with the asymptotic absorption maximum reached at high temperature representing the pure single stranded form.

The analysis of the melting curve was based on a so-called two-state model, essentially implying that at any given stage the solution was composed of double stranded (ds) and single stranded (ss) DNA. This "all-or-none" assumption implied the absence of partially separated forms at all stages, and the mid-point of the melting curve was considered to represent a 1:1 mixture of ds and ss-DNA. The temperature corresponding to the mid-point (T_m) was believed to indicate the thermodynamic stability of the DNA molecule in question, and was widely employed to obtain estimates of the stability of the Watson-Crick base pairs.

A detailed critique of the theory and practice of nucleic acid melting has been presented before [9], there being essentially two problems with the currently accepted model. Firstly, there is reasonably convincing evidence for the presence of ss-DNA even at room temperatures, in equilibrium with ds-DNA, although the percent composition of the mixture is difficult to estimate. Secondly, quantitative approaches are stymied by the difficulty of estimating the extent of dissociation of ds-DNA and consequently the equilibrium constant.

Thus, increasing the concentration leads to a decrease in the absorbance, at room temperature! This indicates the presence of both ss and ds-DNA, with a shift of the equilibrium at higher concentration towards ds-DNA (which has a lower extinction coefficient). By this reasoning, the melting curves at various concentrations should appear as in Fig. 1b, as the fully separated ss-DNA should have a higher absorbance for the case of a higher starting concentration.

These arguments, therefore, cast serious doubt on the melting exercise as a whole, particularly the assumption that the midpoint of the melting curve represents the half-way stage in the conversion of ds-DNA to ss-DNA. It is on this basis that the midpoint temperature (T_m) has been employed in applying the van't Hoff equation [10], leading to quantitative estimates of the Gibbs energy and related thermodynamic quantities. This quantitative treatment now appears invalid in light of the above arguments.

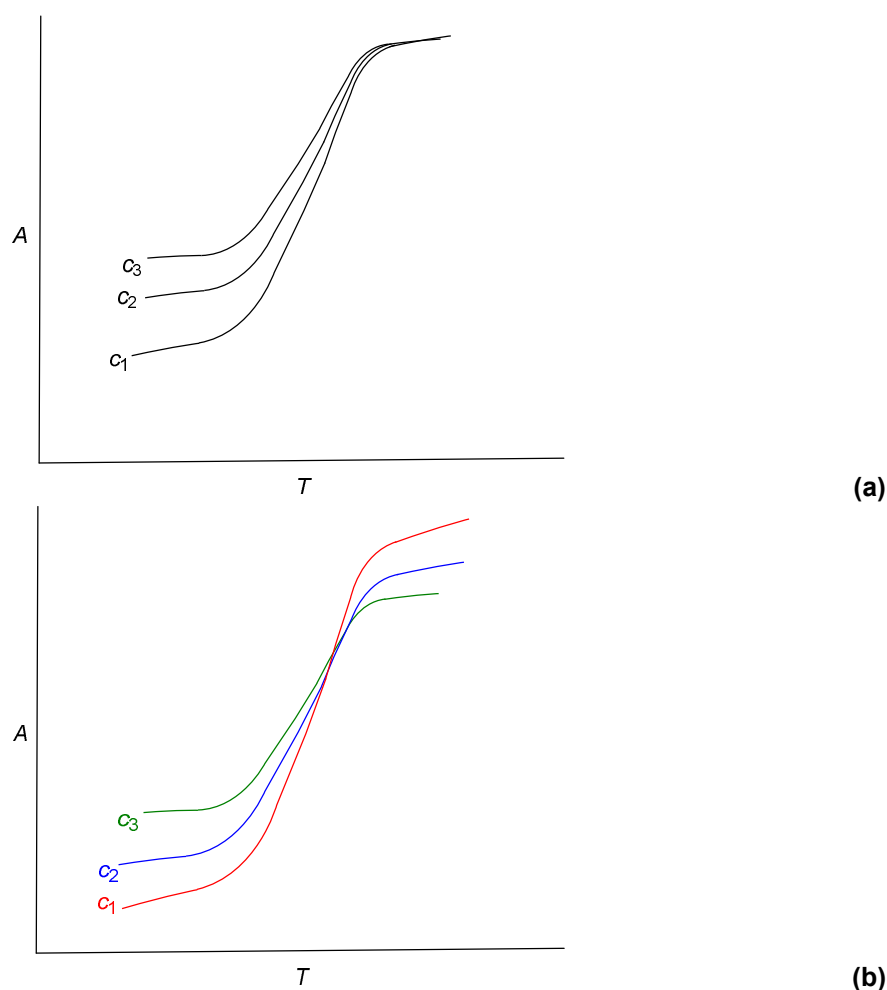


Fig. 1. (a) Typical DNA melting curves obtained at various concentrations c ; (b) the melting curves as they would be if the melting were complete; A is absorbance, T absolute temperature, $c_1 > c_2 > c_3$ in both cases; reproduced from ref. 9

In fact, it seems highly likely that the thermodynamic barrier for the conversion of ds-DNA to ss-DNA is far too high for the melting exercise to be meaningful. It has been proposed that the thermal conversion of ds-DNA to ss-DNA is prohibited, both kinetically and thermodynamically, by the additivity of the base-pairing energies in the duplex [6]. Thus, each base pair contributes ~ 5 kcal mol $^{-1}$ on average, so the overall thermodynamic requirement would be $\sim 5n$ kcal mol $^{-1}$, where n is the number of base pairs in the duplex, with the kinetic barrier exceeding this value.

Solvation effects, however, would moderate these barriers, as indeed observed in the concentration effects mentioned above. In fact, these indicate that solvation has a major influence on the equilibrium between ds-DNA and ss-DNA, which can largely override the

effect of mere heating. Thus, there appears little doubt that ss-DNA is present in solution, possibly in considerable amounts and that, remarkably, the equilibrium can be shifted more easily by concentration changes than by heating!

These arguments then raise the question of what the observed changes in the melting experiments mean. A very likely possibility is that they are the result of the uncoiling of the ss-DNA already present, rather than the dissociation of the ds-DNA. ss-DNA would be expected to behave rather like RNA in preferring to form intramolecular base pairs via self-coiling, which would be reversed by heating. It is also noteworthy that the concentration effects on the absorbance mentioned above (Fig. 1a and b), cannot be the result of the uncoiling of ss-DNA, as an intramolecular process is essentially unaffected by concentration changes.

Finally, it is noteworthy that the thermodynamic stability of the Watson-Crick base pairs as measured by the DNA melting technique now stands invalidated, in view of the above serious ambiguities in the technique itself. Indeed, several of these values were apparently anomalous, most intriguingly the vanishingly small estimate of the G-C base pair strength [11]. In fact, the estimates of the base pair strengths indicated by a kinetic analysis of DNA polymerase action are possibly enormous, as discussed in the following section.

2.1.3 DNA polymerase action

The DNA polymerases constitute a family of closely related enzymes (henceforth “DNA polymerase”), which catalyze the synthesis of DNA oligomers from nucleotides, essentially by forming the phosphodiester bonds of the DNA backbone. In vivo, DNA polymerase accomplishes the replication of DNA that must accompany cell division, so DNA polymerase is of fundamental importance in the sustenance and propagation of all life. Understanding the mechanism of action of DNA polymerase, therefore, acquires supreme importance.

The broad features of DNA polymerase action are indeed well understood [12]. All DNA polymerases possess a “polymerase site” that catalyzes the addition of a new nucleotide by forming a phosphodiester bond. A particularly

critical feature therein is the high fidelity with which it ensures Watson-Crick base pairing in the replication process. This begins with the separation of the double helix of the DNA molecule to be replicated, which provides the template strand required for the action of the DNA polymerase.

The growth of a new strand that is complementary to the template strand ensues, very high accuracy being achieved by Watson-Crick base pairing at the polymerase active site (which accommodates only complementary base pairs). Despite this, however, the replication process at this stage is not entirely error-free, which would be reflected in the fidelity of the replication. As low fidelity levels lead to the accumulation of mutations in the genome, DNA polymerase has evolved an additional mechanism for enhancing the accuracy of the initial replication process.

This is achieved by an intriguing and fascinating “proof reading” process, in which the misincorporated nucleotide is deleted and replaced by the correct nucleotide. The deletion process, however, is accomplished at a site distinct from the polymerase site, the proof reading-excision site being usually a part of the same DNA polymerase molecule. (Some DNA polymerases lack the proof-reading function, in which case a separate enzyme performs the repair function.)

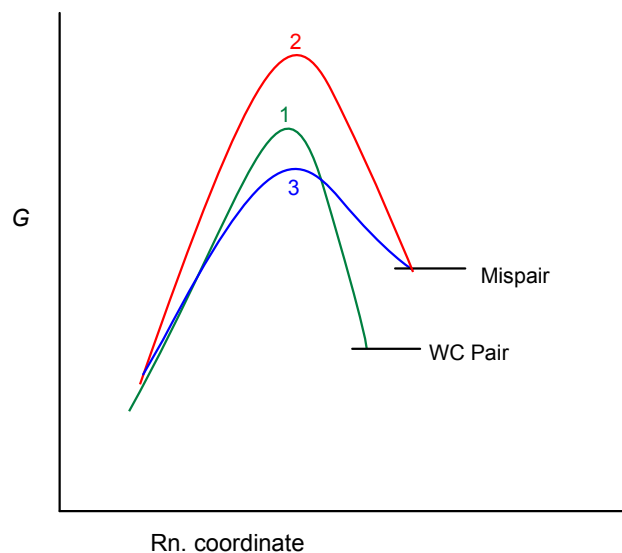


Fig. 2. Gibbs free energy (G) profiles for nucleotide incorporation and excision under DNA polymerase catalysis. Profile 1 (green) represents incorporation of a Watson-Crick (WC) base pair and profile 2 (red) misincorporation, both at the polymerase active site; profile 3 (blue) represents misincorporation (forward reaction) and excision (reverse reaction) at a nuclease site; reproduced from ref.13

The overall process, however, is apparently subject to a mechanistic conundrum involving the principle of microscopic reversibility (PMR) [13]. This arises because the mis-incorporation at the polymerase site and the excision at the proof-reading site imply different pathways for the forward (mis-incorporation) and reverse (excision) processes (Fig. 2). This represents an apparent violation of microscopic reversibility, however, as the excision process is likely much faster than the mis-incorporation process, which thus remains unreversed. Although the PMR is a fundamental principle of chemical kinetics, it is valid only under equilibrium conditions. This requirement is not met in the case of a growing oligonucleotide chain, hence the PMR is evaded.

In fact, this analysis leads to the remarkable revelation that the faster excision function itself is reversible by the PMR! This indicates that mis-incorporation can also occur at the proof-reading site but is avoided by thermodynamic control, thus implying that the Watson-Crick pairs are of overwhelming stability. This conclusion acquires significance in view of earlier doubts about the thermodynamic stability of the Watson-Crick pairs, based on the now discredited DNA melting studies (*vide supra*).

The overall picture that emerges of DNA polymerase catalyzed replication, therefore, is of a complex process although effectively under thermodynamic control. Intriguingly, this raises the question of the reason for the existence of such a complex process involving two different specialized sites. It is possible, of course, that there are limits to enhancing the accuracy of the polymerase site, which operates under kinetic control, hence the need for proof reading and excision. Furthermore, a single polymerase site operating under thermodynamic control would lead to a very slow rate of replication, as it would involve reversible addition and excision of each and every nucleotide. Thus, thermodynamic control at only the proof-reading site is retained, leading to an acceptable balance between rate and accuracy.

2.2 Studies Related to RNA

2.2.1 General considerations

The RNAs function as intermediaries in the translation of the genetic code of DNA to protein. There are essentially two types of RNA involved in converting the DNA codon sequence to protein: messenger RNA (mRNA) and transfer RNA (tRNA). (Although ribosomal RNA or rRNA

is a major form of RNA, its structure-function characteristic is apparently complex and non-specific.) RNAs are overwhelmingly single stranded, a structural feature apparently critical for their role. There are several straightforward reasons for the existence of the two RNAs and their single stranded feature. Thus, the proclivity of DNA to form duplexes would hinder the translation process, so a stable single-stranded molecule that contains the same information as the corresponding DNA is needed. This function is performed by mRNA with its own sequence of codons with which, however, amino acids cannot interact directly. This is the critical operational role performed by tRNA, in "signing off" the complex translation process.

An interesting question is why an unwound DNA duplex cannot perform the same function as mRNA, but it is likely that the core genetic repository needs to be preserved within the protected environment of the cell nucleus. Other intriguing questions pertain to how the enzymes necessary for the biosynthesis of the DNA and RNA—not to mention those involved in the translation process itself—arose in the first place! These conundrums apparently form an awesome philosophical backdrop to the origin of the genetic code.

However, a key question from a structural viewpoint is: what prevents RNAs from forming duplexes like their DNA congeners? A rather obvious answer would refer to the 2' hydroxyl group in the ribose moiety of RNA, as this is the single most important structural difference between DNA and RNA. Thus, an analysis of the steric and electronic effects of the 2' hydroxyl group would be most useful.

2.2.2 The ribosyl-2'-hydroxyl group and its critical role

It is almost certain that steric interactions involving the 2' hydroxyl group in the ribose moiety of RNA are largely responsible for preventing duplex formation although, apparently, these have not been identified with any precision. The solvation of the hydroxyl group would also stabilize the single stranded form relative to the putative duplex.

This "protective" function of the 2' hydroxyl group, however, comes at a price, as the hydroxyl group provides a pathway for the basic hydrolysis of RNA as shown in Fig. 3. Intriguingly, all the same, RNAs appear fairly stable to hydrolysis despite the proximity of the 2'

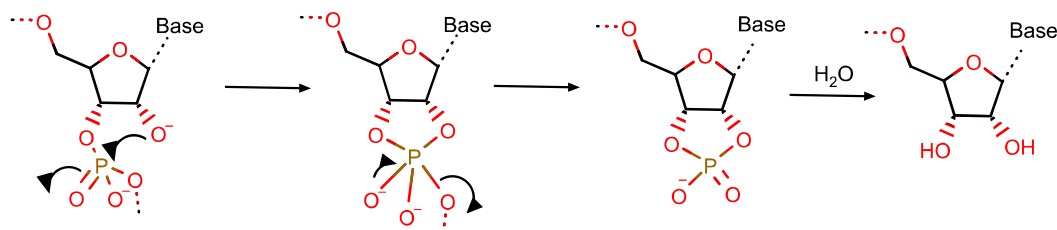


Fig. 3. Mechanism of RNA hydrolysis with intramolecular participation by the ribosyl 2' OH

hydroxyl group to the phosphate group, which could perhaps facilitate the hydrolysis even with mild general bases.

However, reported studies apparently indicate that the acidity of the 2' hydroxyl is relatively depressed, with the estimated pK_a being as high as ~ 16 [14,15]. This is likely the result of lone pair repulsions in the heteroatom rich environment of the 2' hydroxyl group and its putative anion. Thus, a skein of steric and electronic effects apparently confers much needed stability to RNA, towards both duplex formation and basic hydrolysis.

In fact, the proclivity of RNA to remain single stranded is almost certainly the reason for the existence of viruses, which are essentially RNA sheathed in protein. The relative scarcity of DNA-protein complexes is likely due to DNA preferring the duplex form, even if this involves non-canonical base pairing. Analogous duplex RNA is apparently far less stable than the RNA-protein complexes, presumably because proteins are generally sterically less encumbered and demanding than nucleic acids. (By this reasoning, viruses owe their existence to the ribosyl 2' hydroxyl group, to a large extent!)

2.2.3 RNA conformations and structures

The overall shapes of particularly tRNA molecules are critical to understanding their role in protein synthesis, not to mention certain fascinating aspects of the origin of the genetic code itself. The sites of protein synthesis lie in the extranuclear ribosomes, to which mRNA molecules are ferried from the nucleus upon their transcription from DNA (thus converting the DNA codon sequence to the mRNA codon sequence). The translation of mRNA to protein then occurs in the ribosomes by employing tRNA molecules that shuttle in the appropriate amino acids as per the codon sequence on mRNA.

The overall conformation of any RNA would be a balance of several interactions including repulsions between neighboring phosphate groups, base-stacking and self-coiling via base pairing. However, the *in vivo* shapes of RNA molecules are likely enforced in the ribosomal micro-environment to enable their appointed biological function. The single most important structural difference between mRNA and tRNA lies in their overall shapes. Indeed, tRNAs are well known to form two-dimensional cloverleaf secondary structures that fold further to yield L-shaped tertiary structures.

In fact, the enormous size of each tRNA molecule is itself remarkable, indeed raising the question of whether a smaller molecule could perform the same function. The answer, however, apparently lies in the complex translation process, which involves the various tRNA synthetase enzymes corresponding to the tRNAs, in order to charge the tRNA with the appropriate amino acid. Thus, each amino acid corresponds not just to a specific tRNA but also a specific tRNA synthetase. Indeed, without this correspondence the faithful translation of the genetic code to a protein sequence, apparently, would be impossible.

This conclusion, however, is predicated on the need for a large tRNA molecule in which the anticodon is separated—indeed by an enormous distance—from the site of charging of the amino acid (the “CCA tail” end). A possible reason for the need for a large tRNA molecule now becomes apparent, in that this increases the number of interactions between the tRNA and the corresponding tRNA synthetase molecule. This would enhance specificity, thus reducing mis-incorporation of an amino acid in the growing polypeptide chain. (The larger the number of recognition sites the greater the specificity of the interaction between host and guest molecules.)

Intriguingly, in fact, this raises the possibility of severe steric clashes between neighboring tRNA-tRNA synthetase complexes, during translation along the mRNA chain. However, this may be avoided by twisting along the mRNA sugar-phosphate backbone, so that the neighboring complexes are mutually skewed or staggered (the acyclic bonds along the backbone possessing free rotation).

Clearly, fidelity at all stages in the life cycle of a cell—from genome replication to protein synthesis—is critical to the survival of the organism as a whole. Apparently, Nature has evolved a fascinating system of checks and balances, from proof-reading during replication to the complex tertiary structures of the tRNAs, in order to ensure greatest possible fidelity in transcription and translation.

2.2.4 Evolutionary implications of replication, transcription and translation

The functioning of the genetic code—essentially involving replication, transcription and translation—leads to the key dogma that biological information flows in the direction DNA→RNA→protein. However, this raises fascinating questions about both the genetic code itself and its origin in the primordial earth. A particularly intriguing question concerns the fact that the final translation of the codon sequences in DNA into protein requires the intermediacy of specific tRNA synthetases that are themselves proteins. Hence, the view that DNA is the sole genetic repository is apparently an oversimplification. In other words, “codon-anticodon-tRNA synthetase” form a set, its constituents needing to be considered together for the genetic code to have any practical meaning.

The intimate involvement of the proteinic tRNA synthetases in the translation of the genetic code leads to a chicken-vs.-egg philosophical conundrum about which arose first, *i.e.* nucleic acid or protein. In fact, the dogma (DNA→RNA→protein) is upheld under current conditions of the evolved biosphere only if questions about the origin of the proteins involved in the dogma itself are not raised: These proteins involve not only the tRNA synthetases but also the various enzymes involved in the biosynthesis of the nucleic acid components themselves! In this sense, the dogma is practically an article of faith!

This conundrum indeed encapsulates—at the molecular level—the eternal question about the origin of life itself. A resolution of the conundrum is only possible if it can be proven that either nucleic acids or proteins could have been the earliest informational systems. This implies that either of these can encode, self-organize and self-replicate, without involving the other. A combined nucleic acid-protein informational system—as obtains currently—could have evolved subsequently.

As nucleic acids are also known to possess catalytic properties it would appear they arose first, as implied in the RNA-world hypothesis [16]. However, the relative instability of nucleic acids raises the question of whether they would have survived the harsh conditions of the primordial earth. The phosphorus centers of the nucleic acid backbone are notoriously prone to nucleophilic attack, although the *in vitro* evidence about this is apparently debatable [17].

Alternatively, the earliest informational macromolecules may well have been proteins, noting the enormous stability of the peptide bond. Indeed, proteins are widespread if not ubiquitous in the present biosphere (as are carbohydrates), whereas nucleic acids are ensconced in the protected environment of the nucleus. However, an initial protein-only world poses a challenge to the vastly popular RNA-world hypothesis, although this may need to be reassessed [18,19].

In fact, the abiotic synthesis of amino acids and their polymerization would be far more straightforward than the abiotic synthesis of the nucleic acids. The latter has a greater number of components (sugar, base and phosphate), with the organic sugars and bases themselves having to be abiotically synthesized. These considerations, apart from the relative stability of proteins, apparently favor the possibility that life arose from abiotically generated proteins.

The RNA-world hypothesis apparently assumes that “non-random” protein synthesis needs a template, thus ruling out an initial protein-only scenario. However, protein synthesis in the absence of a template need not be completely random, and could be driven by considerations of kinetic and thermodynamic stability of the formed proteins. (This would include autocatalysis, also noting that the amino acid sequences in the abiotic proteins represent accrued information acquired without involving a template!) An early protein world, however, raises the question of

how and when the transition to the current genomic system occurred.

An interesting possibility is that an intermediate phase involving both proteins and nucleic acids as informational macromolecules set the stage for further molecular evolution to the current state (tRNA synthetases being relics of this phase). Primitive proteins—the earliest enzymes—could have catalyzed the abiotic synthesis of the nucleic acid components, leading via their oligomerization to protein-nucleic acid complexes and hybrids.

The next obvious step would have employed nucleic acids as templates for the synthesis of both proteins and nucleic acids themselves — a stage rather familiar to modern humans! Furthermore, the question of whether life—in whatever form—could have arisen from the abiotic synthesis of other precursors leads to considerations of “intelligent design”, which is perhaps philosophically fascinating but beyond the scope of this paper!

3. CONCLUSION

There are several aspects of nucleic acid structure and function that need to be urgently addressed and possibly reassessed. In particular, the status of the DNA double helix in the solution state needs to be reviewed in light of the glaring inconsistencies in the DNA melting studies, which are not only ambiguous but lead to practically invalid conclusions. In fact, there is much evidence to indicate that the DNA double helix unravels in solution, leading to a mixture of double and single stranded forms that responds to concentration changes but not—intriguingly—to heating. The observed changes upon heating are compatible with the partial unwinding of the duplex, followed by uncoiling of the resulting single stranded forms.

Certain aspects of the action of DNA polymerase remain intriguing. Thus, its proof-reading function represents an apparent evasion of the principle of microscopic reversibility, as the nucleotide insertion and the reverse excision occur via different routes. However, a closer examination of the reaction mechanism leads to critical insights into the origin of the high fidelity of DNA replication. Thus, DNA polymerase apparently employs a combination of kinetic control (at the polymerase site) and thermodynamic control (at the excision site) that minimizes the rate of

nucleotide misincorporation in the overall replication process.

Several aspects of the structure and stability of the RNAs, which are key intermediaries in the transfer of genetic information per the central dogma (DNA→RNA→protein), are intriguing. In fact, RNA likely owes its hydrolytic stability to both the steric inaccessibility of the ribosyl 2' hydroxyl group as also its possibly depressed acidity. The steric effect at the 2' hydroxyl group is also the likely reason for the relative absence of RNA duplexes. The relatively large size of a tRNA molecule is indeed intriguing, but likely results in greater specificity in its interaction with the corresponding tRNA synthetase molecule, thus minimizing amino acid mis-incorporation and leading to higher fidelity in the translation process.

Several evolutionary aspects of the central dogma (DNA→RNA→protein) are fascinating as they lead to the eternal question about the origin of life itself. In fact, the critical and intimate involvement of the tRNA synthetases in the translation of the genetic code raises doubts about the central dogma, as the genetic code is practically meaningless in the absence of protein. This apparently leads to two distinct origin of life scenarios, based on either protein or nucleic acid as the progenitor macromolecule. The considerable stability of proteins relative to nucleic acids, however, indicates that primitive proteins were likely the earliest informational macromolecules that could also catalyze the abiotic synthesis of the nucleic acid components. An intermediate stage during which protein-nucleic acid hybrids evolved further towards the current biosphere seems likely to have occurred.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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