Prebiotic Chemistry

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Looking Beyond the RNA Structural Neighborhood for Potentially Primordial Genetic Systems**

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Prebiotic chemistry can be defined as the chemistry needed to "kick-start" biology from inanimate organic matter.[1] Once a minimum level of biology is reached, then evolution, according to the Darwin–Wallace mechanisms at the molecular level, can be relied upon to optimize the system.[2] Prebiotic chemistry is therefore essentially a search for processes in which organic matter may be brought to life through self-organization. The problem with this search is that, at every step of the way, it is difficult to know which path to follow without getting lost in a labyrinth of chemical complexity. Prebiotic chemists need all the guidance they can get from biology and their own well-designed chemical experiments (Figure 1).

Figure 1. Which path to follow? A perennial problem for prebiotic chemists.

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Contemporary biology is based on the code contained in nucleic acids, which exemplify the concept of self-organization of organic matter, as each strand of a duplex can potentially act as a template for the assembly of the other from monomers or short oligomers.[3] A major goal of prebiotic chemistry has therefore been the demonstration of routes to either RNA or DNA from simple feedstock molecules. In the early days it was not clear which of these to target, but recent spectacular advances in biology have added great support to the "RNA world" hypothesis,[4] and chemists have accordingly tried to find prebiotically plausible "predisposed" routes to this nucleic acid, although to no avail. In the last few years, therefore, the seemingly insurmountable difficulties encountered in the prebiotic synthesis of RNA have prompted a search for other potentially primordial information-carrying oligomers.[5] The hope is that a system will be uncovered that is capable of supporting genetics, and is readily derived from prebiotic feedstock molecules by a process of constitutional self-assembly. If such a system is found, its suitability for biological processes can be explored with a view to establishing whether it could have subsequently spawned an RNA world. Cairns-Smith, one of the first advocates of this general approach, envisaged a mineral origin of life.[6] However, the structural dissimilarity of clays and RNA makes a transition from the one to the other—or "genetic takeover" as Cairns-Smith called it—appear unlikely. More recently, the creativity and synthetic power of organic chemists have been brought to bear on the problem, and many nucleic acid variants structurally closely related to RNA have been made and functionally evaluated.[7] These studies have revealed that there are several sugar–phosphate backbones which present the attached canonical nucleobases in such a way that Watson–Crick base pairing between oligomers is possible. Furthermore, pairing between nucleobases attached to different backbones is often feasible, thus allowing for the attractive possibility of the transference of information between different macromolecular types. However, for a system to be accepted as prebiotically plausible, its generational chemistry—that is how it might self-assemble—must be considered. The problem of how these alternative nucleic acids might have been generated by prebiotic chemistry has been left largely unaddressed,[8] and so experimental assessment of their generational complexity is lacking. On initial inspection, however, none of these alternatives appear simpler than RNA. In particular, the attachment of the nucleobases to the sugars or sugar phosphates by glycosidation appears as unfeasible for these alternative nucleic acids as it does for RNA.[9] Since the canonical nucleobases are relatively easily generated as free heterocycles,[10] this inability to attach them to sugars is a major stumbling block in the prebiotic synthesis of nucleic acids. So, if the nucleobases are easy to make but difficult to attach to sugars, then why not posit informational oligomers based on alternative backbones such as oligoamides and oligopeptides? Such oligomers are constitutionally quite distinct from RNA but many have been made and shown to pair with each other and even sometimes with RNA,[11] but again generational studies are lacking, so it is

not actually known if it would be any easier to attach the nucleobases in these cases. It has thus become apparent that a very large number of information-carrying oligomers which undergo Watson–Crick base pairing can be constructed using the natural nucleobases, but there is no indication that any are simpler to generate than RNA.

In current studies by the Eschenmoser research group,[12] information-carrying oligomers that are constitutionally very remote from RNA are identified using simple structural criteria for the backbone to ensure conformations conducive to pairing. Furthermore, ease of backbone attachment and other generational considerations suggest the plausibility of recognition elements other than the canonical nucleobases (Scheme 1).

Having identified these and other triazine- and aminopyrimidine-tagged oligo(dipeptide)s and oligo(dipeptoid)s as potential primordial information-carrying oligomers, Eschenmoser and coworkers used conventional organic synthesis to prepare the materials, and then made a comprehensive study of their base-pairing behavior. As predicted, but nonetheless remarkably, the newly prepared oligomers were found to base pair to themselves and to the nucleic acids, RNA and DNA. However, the pairing throughout the series was not perfect, and neither the triazine nor the aminopyrimidine system was found to pair strongly across the range of heterocyclic substitution patterns from diamino to dioxo. Interestingly, the diaminotriazine **1** and the dioxoamidopyrimidine **2** were strong pairing elements, whilst the dioxotriazine **3** and the diaminoamidopyrimidine **4** were not. In other words, according to stringent functional criteria, the base pairing of triazine and aminopyrimidine systems are not expected to be, or to have been, individually capable of supporting genetics. A mixed system which comprises the best elements of both is possible, but its prebiotic likelihood is diminished by significantly increased complications in the generational chemistry.

From, a prebiotic perspective, the results reported by the Eschenmoser research group are very important for two main reasons. Firstly, they point to the comparative ease with which it is possible to find functional and prebiotically plausible backbones for information-carrying oligomers if careful attention is paid to structural and generational selection criteria. Secondly, they highlight the functional superiority of the natural nucleobases over other recognition elements of comparable simplicity for generation. As regards the future path that should be followed (Figure 1), the indication is that in future we should focus on systems based on the natural nucleobases and look for a potential RNA precursor that is easily produced by constitutional self-assembly. However, since any scenario involving an RNA precursor additionally faces the problem of the transition to RNA-based biology,[13] then we would probably also do well to have another look at RNA itself. Perhaps the seemingly insurmountable problems in the prebiotic synthesis of RNA can be overcome.

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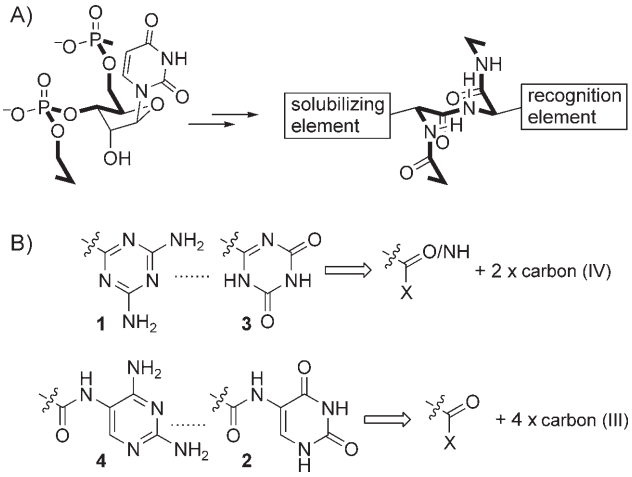

Scheme 1. Selection of new information-carrying oligomer systems.[12] A) "Back-of-an-envelope" selection criteria starting from RNA. Two of the main-chain bonds of the RNA backbone have 180° torsional angles, so if these are replaced with *trans* double bonds or equivalents, new backbones having similar structural constraints should result. Amide-based backbones such as the one shown fulfill this criterion and are appealing because of the generational simplicity of the structural components of α-amino acids. Recognition elements are positioned so that they can be regularly presented by the oligo(dipeptide) backbone in much the same way that the canonical nucleobases of RNA are presented by its ribose phosphate backbone. To ensure solubility in water, the backbone is additionally decorated with charged solubilizing groups. B) Recognition elements which were selected both for their likely pairing ability and on the basis of generational considerations. The triazines can be seen to derive—at least in theory—from a carboxylic acid derivative on an amino acid side chain and two one-carbon units at oxidation level IV (for example, H_2NCN). The 2,4-disubstituted 5-aminopyrimidines potentially derive from four one-carbon units at oxidation level III (for example, HCN), and their attachment to the side chain of the amino acid is through the most nucleophilic group of the heterocycle.

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