

# On the role of the molecular recognition principles in astrobiology

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## ABSTRACT

Principles of molecular recognition, which include both intra- and inter-molecular noncovalent interactions, guide two- and three-dimensional organization of molecules which is critical for functioning and evolution of life. In this paper we review the importance of the noncovalent interactions in the genetic systems with an emphasis on the ionic interactions. We review the most recent work on the metal- RNA interactions, which shows how such interactions were intimately connected with the environment on the early Earth. We also bring up the proposals by others of the requirements for the extraterrestrial genetic systems which are not based on RNA or DNA. Such systems would utilize the available non-covalent interactions for their stabilization and molecular recognition in general in a manner which could be different than that on the Earth.

**Keywords:** molecular recognition, noncovalent interactions, RNA world, extraterrestrial genetic systems, chemical evolution of molecular recognition

## 1. INTRODUCTION

We first briefly review the basic principles of noncovalent interactions which are at the heart of the molecular recognition. Then we review selected noncovalent interactions which are involved in the functioning of the genetic systems on Earth. We then address ionic interactions that were likely involved in the early RNA world. Chemical evolution of the ionic noncovalent interactions between the RNA and metals in its primordial environment likely preceded the modern RNA-ion interactions. We review the proposals of the extraterrestrial genetic systems which are not based on RNA and DNA. Some such systems would need to use different noncovalent interactions for their stabilization and for the molecular recognition with other species.

## 2. MOLECULAR RECOGNITION

We start with the nomenclature which is used in the field. Terms such as host-guest chemistry, supramolecular chemistry and self-assembly refer to the intermolecular processes. The term molecular recognition includes both inter- and intramolecular interactions. This term describes the phenomena that are controlled by specific noncovalent interactions<sup>1</sup>. A more detailed explanation of noncovalent interactions follows. These are interactions in which electrons stay paired in reactants and products, and there is no change in the type of chemical bonding in these interacting species<sup>2</sup>. The intrinsic nature of non-covalent interactions is difficult to pin down since these bonds are weaker and are much more sensitive to the environment than the covalent bonds<sup>2</sup>. It is important to note that these weak noncovalent interactions can be demonstrated experimentally and can be studied quite effectively via theoretical calculations. Examples include matrix isolation IR, gas-phase IR, and microwave spectroscopy, among others<sup>2</sup>. In many such interactions the electrostatic energy is the key energy component. The directionality of the electrostatic component can be used to predict the directionality of noncovalent interactions. These interactions are considered in general to be weak, ranging from very weak (less than 1 kcal/mol) to reasonably strong, such as the familiar hydrogen bond (H-bond), which is about 5 kcal/mol. Weak molecular complexes are formed with aryl groups (Ar), in which Ar acts as an electron donor<sup>2</sup>.

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The effect of the weak noncovalent interactions is cumulative. A dramatic example of this applies to geckos, which have the ability to adhere to and move rapidly on the vertical walls<sup>3</sup>. Gecko's feet have several thousand keratinous hairs. Each of these contains hundreds of tips. These create millions of hydrophobic centers which can lead to adhesion to both hydrophilic and hydrophobic interactions via weak Van der Waals noncovalent interactions. Other electrostatic noncovalent interactions are H-bonding and charge transfer<sup>3</sup>. The pi-pi interactions (face-to-face and face-to-edge) include pi-cation, CH-pi and pi-facial H-bonds. Examples of these can be found between the amino acid side chains<sup>4</sup>. Generally, for peptide-peptide molecular recognition the ionic interactions, H-bonding, hydrophobic interactions and pi-stacking are considered<sup>5</sup>. The ionic interactions are the basis of a strategy in which one helix is + charged and the other is -. Such intermolecular interactions can be controlled by the changes in pH and salt concentrations. Studies of the noncovalent interactions as related to the enzymes and receptors<sup>6</sup>, to the halogen-Ar interactions that are involved to the protein ligand binding<sup>7</sup>, and to the use of the general theoretical and experimental approaches<sup>8</sup>, are some selected examples of the voluminous work on this topic. In this paper we focus on the ionic noncovalent interactions in the genetic systems. They are critical for the stability, shape and catalytic ability of RNA both in the proposed early RNA world and in the present times<sup>9-10</sup>. We shall also review how chemical evolution of the ion-RNA relationship occurred.

### 3. IONIC NONCOVALENT INTERACTIONS IN NUCLEIC ACIDS

RNA is the central molecule in the theory of the origins of life. It is currently believed that RNA was the original self-replicating molecule which had both the ability to preserve and transmit information and to act as a catalyst<sup>9-10</sup>. RNA is a ribonucleic acid polymer. Its units are sugar ribose, a nucleobase, and a phosphate. Sugar-nucleobase unit is termed a nucleoside. Structure of the nucleoside adenosine is shown in Fig. 1. Upon inclusion of the phosphate group a nucleoside become a nucleotide. An example is shown in Fig. 2<sup>10</sup>.

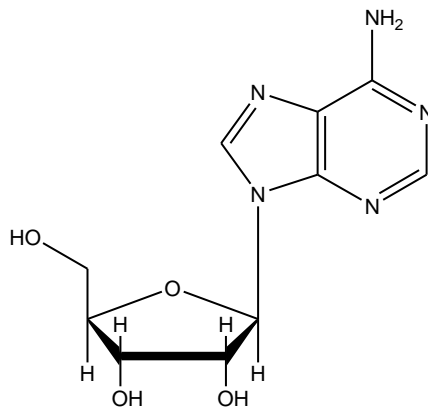


Figure 1. An example of a nucleoside (adenosine) in which the nucleobase adenine is joined to the sugar ribose.

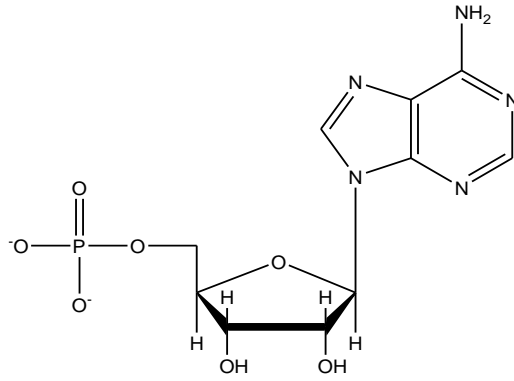


Figure 2. An example of a nucleotide (adenosine monophosphate) in which the nucleoside from Fig. 1 acquires a phosphate group.

The formation of the nucleic acid polymer occurs via phosphate bonds. Figure 3 shows a dinucleotide, thus just two units, but it illustrates the principle.

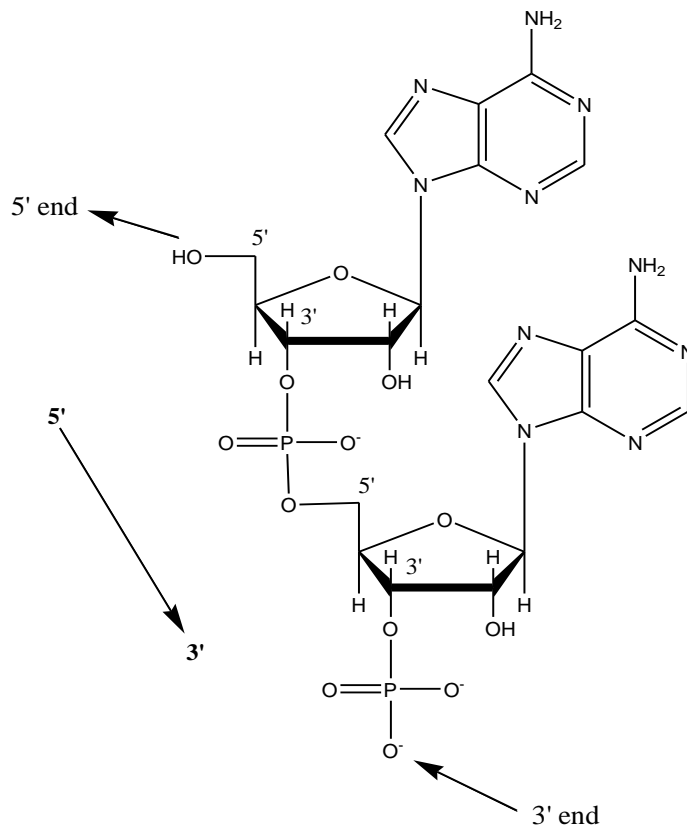


Figure 3. The structure of a dinucleotide, which shows how polymerization occurs via phosphate bonds.

From these relatively simple structures we can see that the issue of noncovalent interactions is further complicated by the fact that the organic molecules have a potential for forming multiple noncovalent interactions. More often than not it is difficult to entangle these. From the structures in Figures 1 and 2 we see that a nucleobase, in this case adenine, can form H-bonds. The phosphate group from the nucleotide has the ability to polymerize and create a long phosphate backbone, which is negatively charged. The long oligonucleotide chains fold and create complicated 3-D structures<sup>10</sup>. The DNA has deoxyribose as a sugar. Its overall folding properties differ from those of RNA because of the change in the sugar structure.

Benner has analyzed the structure of DNA and has proposed that the charged backbone may be a universal requirement for any genetic system in water<sup>11</sup>. The repeating charges force the interactions between the strands away from each other. The reason is the repulsion of charged phosphate groups in the backbone. The nucleobases are pushed towards each other, away from the backbone. The nucleobases make the well-known hydrogen bonds among themselves, but the polyanionic backbone is still the dominant physical property of DNA. Further, Benner states that the repeating charges keep the DNA strands from folding. The support for this came from the sulfone-linked long RNA chains, which do not have a repeated charge, and which indeed fold and aggregate. Most importantly, the repeating charges allow DNA to support Darwinian evolution. For such evolution to occur, replication is required but is not sufficient. The Darwinian systems must also generate inexact replicates which create diversity upon which selection acts. The polyanionic backbone dominates the physical properties of DNA. Thus, replacing one nucleobase with another will create diversity but the essential conditions for replication will be maintained by the backbone. This was supported by the behavior of the synthetic analogs of DNA with peptide-linked nucleic acid (PNA). These structures lack the repeating charge, and are not amenable to evolution of uncharged DNA analogues. Small changes in PNAs often result in a large change in physical properties, sometimes causing even a precipitation. Thus, Benner states that the alternative life must have a charged backbone, polyanionic, like the life on Earth, but could also have a polycationic one. Much more is covered in Benner's paper, such as the requirements for the nucleobases. We focus just on the backbone, since it illustrates dramatically how a complicated genetic system is controlled by a simple ionic interaction.

#### **4. INTERACTION OF IONS WITH NUCLEIC ACIDS**

This topic is very important since it represents a bridge between the nucleic acids and the inorganic ions from the environment. The ions are intimately involved in the structure and functioning of nucleic acids. There is a large literature on this subject, from which we single out the most recent work which points out to the chemical evolution of the nucleic acid – ion interactions. The role of the metal ions in RNA catalysis is covered in depth in ref.<sup>12</sup>. The ability of RNA to perform its catalytic function is dependent on metal ions. The favored ion is  $Mg^{2+}$ <sup>12-13</sup>. The paper<sup>12</sup> surveys many other ions and discusses the mechanism by which the ions are involved in the RNA catalysis. The surprise comes with the new work in which  $Mg^{2+}$  is substituted with  $Fe^{2+}$ <sup>14-15</sup>. The resulting  $Fe^{2+}$  RNA is now also catalytic, but the new function has the potential to perform the oxido-reductions.  $Fe^{2+}$  ion was abundant on the early Earth, and was probably part of the original RNA world. Only later, when the changes in the early Earth atmosphere became oxidizing, was the  $Mg^{2+}$  introduced as a substitute. This presents a clear example of chemical evolution of RNA-metal system. This evolution was dictated by the environmental conditions on Earth.

#### **5. IMPLICATIONS FOR THE SEARCH FOR EXTRATERRESTRIAL LIFE**

We can see that there are underlying principles in the design of the genetic system on Earth. We have singled out the features which are controlled by a simple noncovalent interaction, namely the ionic interaction. Some critical features of the genetic system, such as the requirement for the repeated charges in the backbone, may be relevant to the extraterrestrial life, if it occurs in water, but instead of the polyanions which we have on Earth, we may have polycations. The three dimensional structure of the polynucleotides on Earth, which is our genetic material, necessitates interactions with ions, thus again, a simple noncovalent ionic interaction. However, it was found recently that the choice of the ions may have been dictated by the conditions on the early Earth, and as such may not be necessarily transferrable to the extraterrestrial life.

## 6. CONCLUSIONS

In this paper we have brought to the attention the importance of the ionic noncovalent interactions as a key to the molecular recognition within genetic system on Earth. Due to the repulsions of the polyphosphate chains in DNA, for example, the H-bonding between the nucleobases is reinforced. The ionic repulsions create the stability factor in the structure of DNA. In the RNA world the ionic interactions with metals showed chemical evolution. The latter was dependent on the conditions on early Earth. While  $Mg^{2+}$  ion is predominant ion which has a role in folding, stabilization and catalysis of RNA at this time, in the past, it could have been  $Fe^{2+}$ , which was abundant on early Earth. The  $Fe^{2+}$  ion would have expanded the RNA catalytic repertoire to include redox reactions. After the conditions on the Earth changed to oxidative,  $Mg^{2+}$  replaced  $Fe^{2+}$ . This creates a fascinating example of chemical evolution of the nucleic acid – metal interaction, which was dictated by the environmental conditions. In the case of the extraterrestrial situations, we could keep some of these general principles, but they would have to be modified depending on the available chemical possibilities and the nature of the environment. Thus, the polyanionic backbone of our genetic material could be polycationic for the alien life. Various ions could have paired up with such material. The abundance of the ions in the environment and the nature of the atmosphere in the alien habitats would play a role in the selection of the metals.

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