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**Model of Early Self-Replication Based on Covalent Complementarity  
for a Copolymer of Glycerate-3-Phosphate and Glycerol-3-Phosphate**

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(NASA-CR-182912) MODEL OF EARLY  
SELF-REPLICATION BASED ON COVALENT  
COMPLEMENTARITY FOR A COPOLYMER OF  
GLYCERATE-3-PHOSPHATE AND  
GLYCEROL-3-PHOSPHATE (Salk Institute for

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**Abstract:** Glyceraldehyde-3-phosphate acts as the substrate in a model of early self-replication of a phosphodiester copolymer of glycerate-3-phosphate and glycerol-3-phosphate. This model of self-replication is based on covalent complementarity in which information transfer is mediated by a single covalent bond, in contrast to multiple weak interactions that establish complementarity in nucleic acid replication. This replication model is connected to contemporary biochemistry through its use of glyceraldehyde-3-phosphate, a central metabolite of glycolysis and photosynthesis.

**Key words:** Origin of Life, Molecular Evolution, Self-replication, Glycolysis,  
Molecular Complementarity

**Running title:** Covalent Complementarity

## 1. Introduction

One of the most important questions concerning the origin of life is the nature of the earliest hereditary self-replicating molecule. Although heredity in contemporary life is based on replication of nucleic acids, difficulties encountered in the synthesis of nucleic acids under prebiotic conditions suggest that they may not have been the first replicating molecule (Orgel, 1987; Joyce, 1989). This has led to a search for simpler polymers capable of self-replication that preceded nucleic acids in the origin of life (Spach, 1984; Schwartz and Orgel, 1985; Joyce *et al*, 1987). Here we present a model of an early type of self-replication that involves a copolymer of glyceralate-3-P and glycerol-3-P. Replication of this copolymer uses a novel mechanism — covalent complementarity — which derives its specificity from the formation of a covalent bond instead of hydrogen bonds as in nucleic acids. This model brings together into a single process the origins of self-replication and glycolytic metabolism, since the substrate of copolymer replication is glyceraldehyde-3-P, the central intermediate of glycolysis.

In an effort to understand how chemical energy needed for the origin of life was obtained from the prebiotic environment, we have studied chemical reactions that resemble the first energy-yielding step of glycolysis (Weber, 1984a, 1987a). Since this energy-yielding step involves the oxidation of a glyceraldehyde hemithioacetal to give an "energy-rich" thioester that drives the synthesis of ATP, we investigated the related nonenzymatic oxidation and rearrangement of glyceraldehyde hemithioacetals that yielded respectively glyceroyl and lactoyl thioesters (Weber, 1984a, b), and showed that thioesters could nonenzymatically drive the synthesis of phosphoanhydrides (Weber 1981, 1982). We also examined the autocondensation of the glyceroyl thioester that yielded oligoglyceric acid (Weber, 1987b). As a result of these studies we proposed a model of the origin of life that used glyceraldehyde as the substrate for the synthesis of polyglyceric acid, a presumed primitive autocatalyst (Weber, 1987a). Recently, we described the thermal synthesis, hydrolysis, and solubility properties of polyglyceric acid (Weber, 1988).

## 2. Self-replication by Covalent Complementarity

The model of self-replication described here uses glyceraldehyde-3-P as the substrate for the synthesis of a copolymer of glycerate-3-P and glycerol-3-P having a phosphodiester backbone. In the origin of life process this model is considered as a step in the direction of nucleic acid replication from our previous model based on non-phosphorylated glyceraldehyde. As shown in Fig. 1, replication of this copolymer is presumed to occur by covalent complementarity in which glycerate-3-P and glycerol-3-P residues of the newly synthesized strands are paired through an ester bond to respectively glycerol-3-P and glycerate-3-P residues of the parent strands. This covalent recognition mechanism functions like the noncovalent recognition of A and G by respectively U (or T) and C in nucleic acid replication.

There are several conceivable ways of replicating the copolymer starting with glyceraldehyde and inorganic phosphate. Possibly the simplest imaginable pathway is shown in Fig. 2. This pathway uses the redox disproportionation of glyceraldehyde to drive the synthesis of "energy-rich" phosphoanhydrides (reaction 1). The phosphoanhydrides are first used to phosphorylate glyceraldehyde (reaction 2). Replication of the duplex begins by attack of glycerol-3-P on interstrand esters of the parent duplex. This transesterification attaches monomeric glycerol-3-P as an ester to complementary glycerate-3-P residues of the parent strands (reaction 3). Next glyceraldehyde-3-P forms a hemiacetal with the hydroxyl groups of glycerol-3-P residues liberated by the earlier transesterification reaction. Oxidation of these hemiacetals by a second glyceraldehyde-3-P yields glycerate-3-P monomer linked as an ester to complementary glycerol-3-P residues of the parent strands (reaction 4). This reaction also yields glycerol-3-P for the transesterification (reaction 3). Reactions 3 and 4 align monomers along their complementary residues in the parent strands (reaction 5). Finally, the monomers are joined through phosphodiester linkages giving two duplexes each containing one new and one parent strand (reaction 5). The energy that drives the separation of parent strands comes from the favorable

standard free energy change of reactions 4 and 5 ( $\Delta G^\circ = -17$  kcal/mol). The overall replication process (reaction 6) proceeds with favorable  $\Delta G^\circ$  of - 67 kcal/mol.

The proposed replication pathway in Fig. 2 has one major limitation. Spontaneous hydrolysis of the interstrand esters of the duplex prevents attachment of glycerol-3-P to the parent strand by transesterification (reaction 3). Consequently, the size of copolymer that can be replicated is determined by the ratio of rate of replication to that of hydrolysis. This effect of hydrolysis can be overcome by increasing the replication rate or repairing the interstrand esters. Phosphoanhydrides could be used to drive the repair reaction by activating carboxylic acid groups of the glycerate-3-P residues at the break sites. Possibly, this repair process developed into a new, somewhat more complex, type of replication which differed from that in Fig. 2 by the method of monomer attachment. In this new pathway replication begins by hydrolysis of interstrand esters of the parent duplex. Monomeric glycerol-3-P and glycerate-3-P are then attached to their complementary residues in the parent strands by reactions that use phosphoanhydrides to activate the carboxylic acid groups of glycerate-3-P monomers and glycerate residues of the parent strand. Replication is complete when the aligned monomers are joined through phosphodiester bonds. This pathway compared to that in Fig. 2 requires more phosphoanhydride and an efficient method of using this energy to link monomers to the parent strands. Presumably, the copolymer acted on these reactions as an autocatalyst that controlled its own self-replication. Although it is difficult to evaluate the catalytic capability of the copolymer, it possesses the functional groups (hydroxyl, carboxylic acid, phosphate, and bound metal ions) and a sequence-dependent tertiary structure that are requisites for its catalytic role.

Figure 3 shows a molecular model of the copolymer duplex with strands of the same chirality running antiparallel. The interstrand esters are in the favored planar *trans* conformation (Chatani *et al*, 1968; Brant *et al*, 1969; Cornibert and Marchessault, 1972). Similar models can be constructed with parallel strands of the same chirality, and parallel or antiparallel strands

of opposite chirality. However, each strand must be homochiral for the duplexes to have a regular backbone structure. These model duplexes can also assume a helical form with the interstrand esters in the stable planar *trans* configuration. Self-replication is probably simpler for a duplex with strands of the same chirality than those with strands of opposite chirality because the latter requires a different replication catalyst for each strand. The structure of copolymer resembles in some respects the teichoic acid of *Streptomyces antibioticus* which has a 1,2-poly(glycerolphosphate) backbone (Shashkov *et al*, 1979).

Figure 3 also shows that glycerate-3-P and glycerol-3-P can occupy either strand of the copolymer duplex without significantly disturbing the regularity of the backbone. As seen in Fig. 3 the regularity of the backbone is maintained at the position noted by the arrow where the strand location of glycerate-3-P and glycerol-3-P is opposite that of the rest of the copolymer. This structural feature gives the backbone a sequence-independent regularity that could be essential to a replication catalyst.

Copolymer replication has several characteristics that make it an attractive model of early self-replication. Most importantly it is simple and energetically self-sufficient. Starting with glyceraldehyde and inorganic phosphate, the synthesis and incorporation of a pair of monomers requires a single 3-carbon substrate, 5 different catalytic activities, and no exogenous source of energy. Replication by the covalent mechanism can use small, easily synthesized monomers because information transfer is mediated by a single strong bond. In contrast, information transfer in nucleic acids depends on multiple weak interactions that require large monomers whose synthesis is much more complex (Zubay, 1983).

Self-replication of the copolymer by covalent complementarity also seems very resistant to copying errors. The formation of a mismatched pair by bonding of glycerate-3-P monomer to a glycerate-3-P residue of a parent strand can occur only through a highly unstable carboxylic acid anhydride. Also, a mismatched pair involving glycerol-3-P monomer bonded to a glycerol-3-P

residue through an ether linkage is unlikely, given the chemistry of the model. This property of covalent complementarity could result in accurate replication even with a rudimentary catalyst. Possibly, the selectivity of covalent complementarity could be measured in reactions that use suitably activated monomers and copolymer as a template for the synthesis of a complementary strand. Moreover, there may be other copolymers, not necessarily related to the origin of life, that can act as covalent templates.

Copolymer replication is connected to contemporary biochemistry through its use of glyceraldehyde-3-P, a central metabolite of glycolysis and photosynthesis. Surprisingly, the reaction in Fig. 2 that is ultimately responsible for information transfer in copolymer replication — the formation and oxidation of glyceraldehyde-3-P hemiacetal (reaction 3) — resembles the first energy-yielding reaction of glycolysis. This chemical similarity suggests that both self-replication and glycolytic metabolism could have originated from the same dissipative process, the oxidation of glyceraldehyde-3-P.

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## Figure Legends

### Figure 1

Self-replication by covalent complementarity of a copolymer of glycerate-3-phosphate and glycerol-3-phosphate.

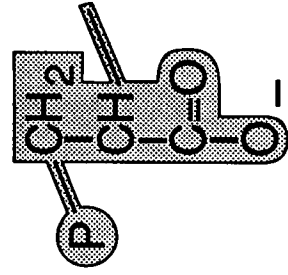
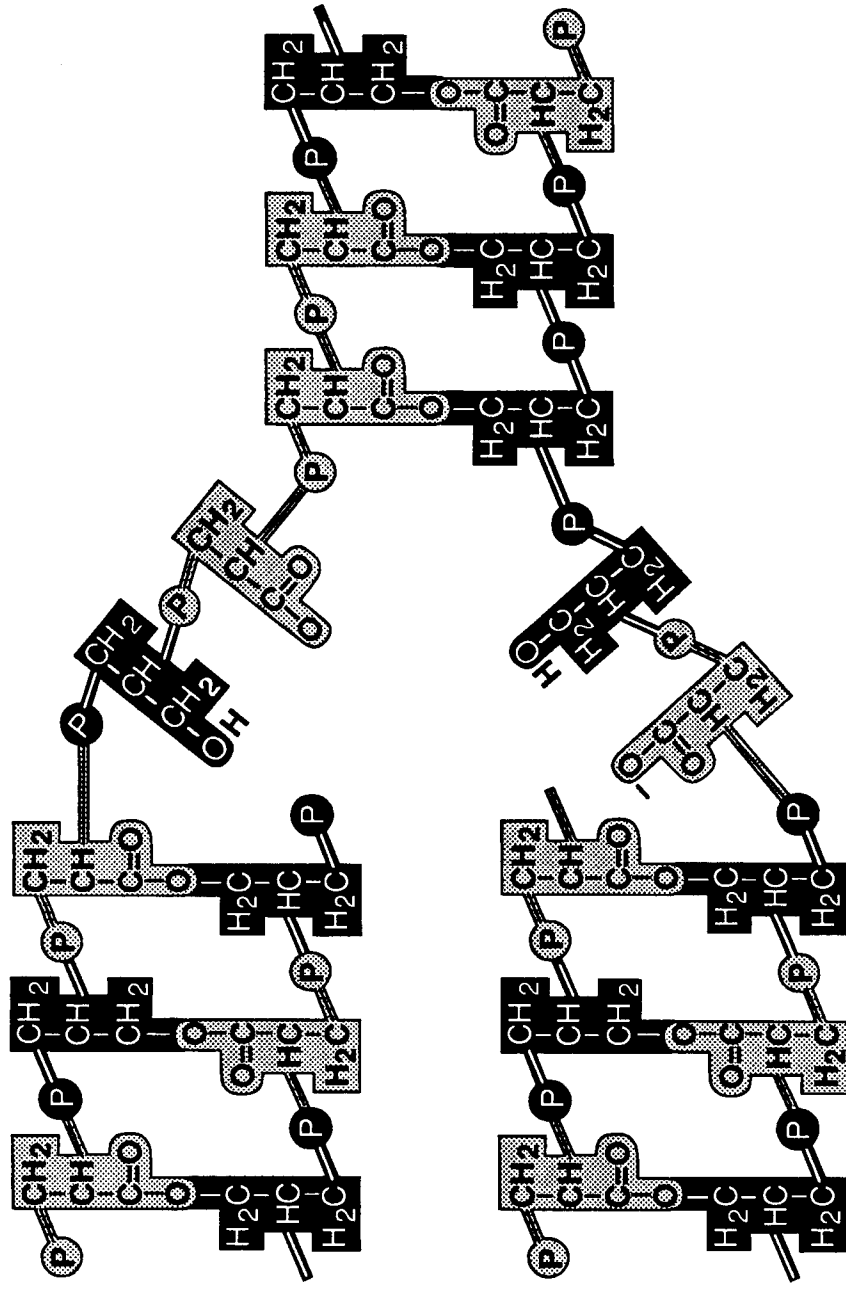
### Figure 2

Reactions for the replication of a copolymer of glycerate-3-phosphate and glycerol-3-phosphate from glyceraldehyde and inorganic phosphate.  $\Delta G^{\circ'}$  is the standard free energy of the reaction at pH 7.0 based on a standard state of 1 M stoichiometric concentration of reactants and products, except hydrogen ion, and on an activity of pure water of 1.0 (Jencks, 1976). The  $\Delta G^{\circ'}$  for the redox disproportionation of glyceraldehyde and glyceraldehyde-3-P are calculated to be -17.6 kcal/mol (Thauer *et al*, 1977). The  $\Delta G^{\circ'}$  for the hydrolysis of the phosphomonoester, phosphodiester, phosphoanhydride (P~P) and interstrand glyceroyl ester are estimated at respectively -2.6 kcal/mol ( $\Delta G^{\circ'}$  of glycerol-3-P hydrolysis (Jencks, 1976)), -4.1 kcal/mol ( $\Delta G^{\circ'}$  calculated for diethylphosphate hydrolysis (Guthrie, 1978; Gerlt *et al*, 1980)), -7.6 kcal/mol ( $\Delta G^{\circ'}$  of ATP hydrolysis (Jencks, 1976)), and -7.6 kcal/mol ( $\Delta G^{\circ'}$  calculated for hydrolysis of the related  $\beta$ -glyceroyl ester of polyglyceric acid (Weber, 1987a)).

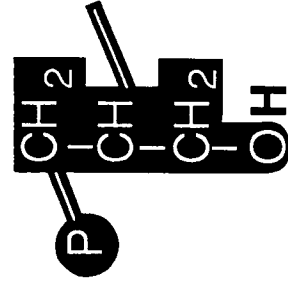
### Figure 3

Antiparallel duplex of complementary copolymers of D-glycerate-3-phosphate and D-glycerol-3-phosphate having a phosphodiester backbone. Along the duplex glycerate-3-P residues in the left strand are joined in an ester bond to glycerol-3-P residues in the right strand, except at the position marked by the arrow where the position of the residues is reversed and a glycerate-3-P residue in the left strand is joined to a glycerol-3-P residue in the right strand.

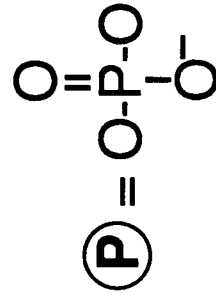




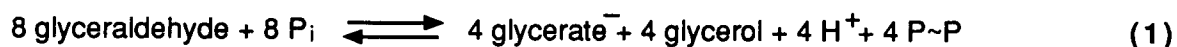
Glyceraldehyde-3-phosphate



Glycerol-3-phosphate



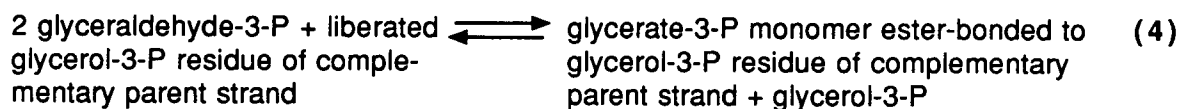
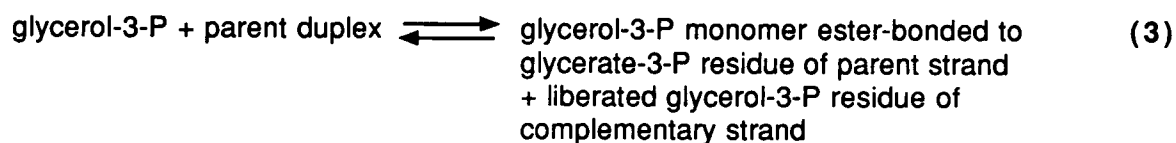
Phosphoanhydride synthesis [ $\Delta G^{\circ'} = -40$  kcal/mol]



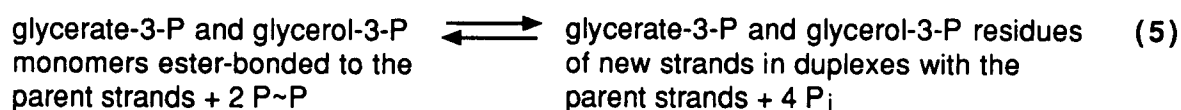
Phosphomonoester synthesis [ $\Delta G^{\circ'} = -10$  kcal/mol]



Monomer attachment [ $\Delta G^{\circ'} = -10$  kcal/mol]

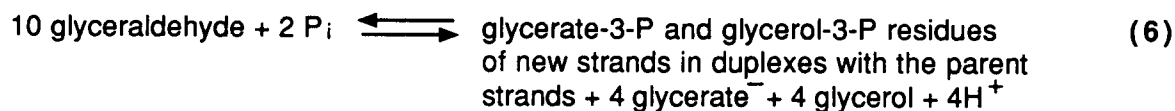


Phosphodiester synthesis [ $\Delta G^{\circ'} = -7$  kcal/mol]



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Net Reaction [ $\Delta G^{\circ'} = -67$  kcal/mol]



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