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Autor: Turian, Gilbert
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PRENUCLEIC NUCLEOBASE PHOSPHORAMIDATES IN THE TRANSITION PRE-RNA – RNA?

BY

Gilbert TURIAN*

ABSTRACT

Prenucleic nucleobase phosphoramidates in the transition pre-RNA – RNA? – The high-energy phosphoramide bond between pre-RNA nucleobases~triphosphates opens in strongly acid conditions by prototropic tautomerization of the nucleobases with subsequent repulsive separation of the now positively charged $N^{+}...^{+}P$ groups. Those would be energetically powered to be bridged by bipolarly hydroxylated, negatively charged 1C – 3C precursors of ribose subsequently complexified to RNA nucleotide.

Key-words: prenucleic, phosphoramide, nucleobases, acid-induced opening, trimetaphosphate cycle.

INTRODUCTION

While there is good evidence to suggest that an RNA-based life form existed at an early stage in evolutionary history, there are several reasons to believe that Darwinian evolution did not begin with RNA (JOYCE, 1989). Life may thus have begun with some simpler replicating pre-RNAs based on "low tech" biochemistry (CAIRNS-SMITH, 1982; SCHWARTZ, 1998), which could have later fallen prey to genetic takeover by RNA (PICCIRILLI, 1995).

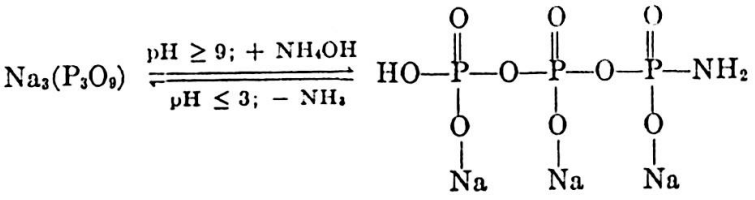
Because of the serious difficulties of D-ribose prebiotic synthesis (JOYCE & ORGEL, 1999), such pre-RNA would be deprived of the pentose. Inspired by the well-known example of creatine-phosphate, we have proposed a model of straight locking of coding nucleobases on phosphate groups of polyphosphate by phosphoramide (P~N) bondings (TURIAN, 1996, 2000), as experimentally confirmed by NMR identification techniques (TURIAN *et al.*, 1998-9; TURIAN & RIVARA-MINTEN, 2001). However, the evolution of such prenucleic polymers to ribonucleic acids necessarily somehow involved the incorporation of ribose precursors further complexified to D-ribose. Consequently, we have first thought (TURIAN, 2001) that available chemical evidence of the pH-controlled locking-opening of the energized P~N bonds of dimeric nucleobase-phosphate could have offered the possibility of their bipolar bridging by ribose precursors secondarily complexified to the "modern" trimeric ribonucleotides of RNAs.

* Microbiologie générale, Département de Biologie végétale, Université de Genève, CH-1211 Genève 4.

1. Acidic opening of the "energy-rich" phosphoramide bonds

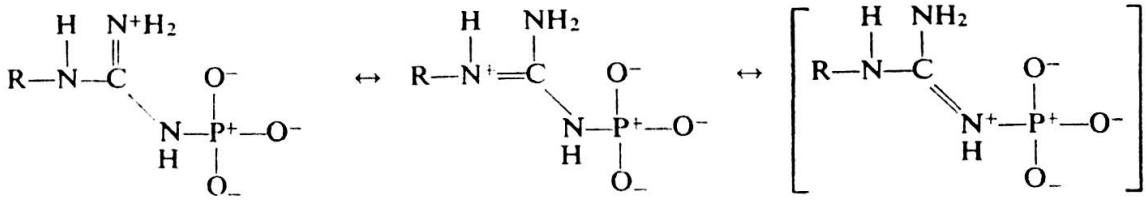
Cyclic tripolyphosphate has been used to convert NH_3 and primary amines to amidophosphates (FELDMANN & THILO, 1964; LETSINGER *et al.*, 1972).

The simplest phosphoramide, amidotriphosphate $Na_3HP_3O_9$-NH_2, produced by condensation of linear triphosphate (TP) with aqueous ammonia, reverts to trimetaphosphate with loss of ammonia on acidifying the solution as already proposed by QUIMBY & FLAUTT, 1958 and THILO, 1962:



In 1958, FRUTON & SIMMONDS had commented that the relatively large negative free-energy change in the hydrolysis of such an "energy-rich" bonded compound as ATP can be attributed to an increased "resonance stability" of the products of hydrolysis, and to electrostatic repulsion between the groups joined by the "energy-rich" bond.

The naturally occurring phosphoguanidines, creatine phosphate and arginine phosphate, are also endowed with "energy-rich" nature largely due to the inhibition of the normal resonance associated with the symmetry of the guanidine ion. In particular, in low pH media, their resonance form, with the positive charge adjacent to the positively charged phosphorus ion, leads to their hydrolysis by repulsion of their similar electric charges, as clearly illustrated for creatine phosphate by MAHLER & CORDES (1969):



The reaction of creatine with ATP to form creatine phosphate and ADP is an example of a reaction in which phosphate transfer from ATP is not accompanied by a negative $\Delta F'$. This reaction is catalyzed by the enzyme ATP-creatine transphosphorylase: its $\Delta F'$ (pH 7.5) has been estimated (from equilibrium studies) to be about +3 kcal, giving a value of $\Delta F'$ of about -11 kcal for the hydrolysis of creatine phosphate to creatine and phosphate (see CORBRIDGE, 1978), again assuming a value of -8 kcal for the hydrolysis of ATP. We can therefore reasonably admit that the P~N bond energy value of our nucleobase phosphates equates that of creatine phosphate.

2. Prototropic tautomerism of nucleobases

In nucleobases, as in the other nitrogen base creatine, the amino groups are only protonated in acidic conditions when the pH of their solvent is lowered to values close to their pKas. Such so-called prototropic tautomerism is accompanied by movements of

protons from one ring nitrogen atom to another one (in pyrimidines double band from $N_{1\text{-}6} \rightarrow N_{6\text{-}5}$, in purines from $N_{9\text{-}8} \rightarrow N_{8\text{-}7}$, see JEFFREY & SAENGER, 1994, p. 237). It is this acid-induced protonation which leads to a repulsion of the two positive molecular poles produced and to the opening of the P~N bond (see § 1).

The formation of a phosphoramide P~N bond between a nucleobase (or imidazole *i* alone) and cyclic triphosphate (TMP) requires a subtle equilibrium between (1) primary prototropic "down tautomerism" of the nucleobase by Mg^{2+} hydrolytically-induced transient acidification in slightly alkaline conditions (TURIAN & RIVARA-MINTEN, 2001) to position the NH_3^+ group for electron pair donation to one electrophilic P and (2) preeminence of alkaline conditions to maintain the "retro(up)tautomerization" of the nucleobase (Fig. 1) and thus the integrity of the P~N bond known to be especially robust at high pH (LOHRMANN & ORGEL, 1973). This fact would be relevant in prebiotic evolution from prenucleic to nucleic compounds when any sharp environmental acidification (pH drop from > 7 to < 5) could open the P~N bond by + ... + repulsion and permit the median insertion of hydroxylated (polyols) precursors of D-ribose (see § 3). Importantly, this type of reversible tautomerism can only happen in P~N bonded phosphoramidates and not occur in the N-C bonded nucleosides when pyrimidine (N_1) or purines (N_9) are substituted by the furanose moiety (JEFFREY & SAENGER, 1994). This fact joint with the known resistance of phosphoester bonds compared to the lability of phosphoramide bonds (see Vogel, 1984), would confer a selective advantage in acid media to the protonucleotide P-C-N over the simple P~N prenucleic phosphoramidate.

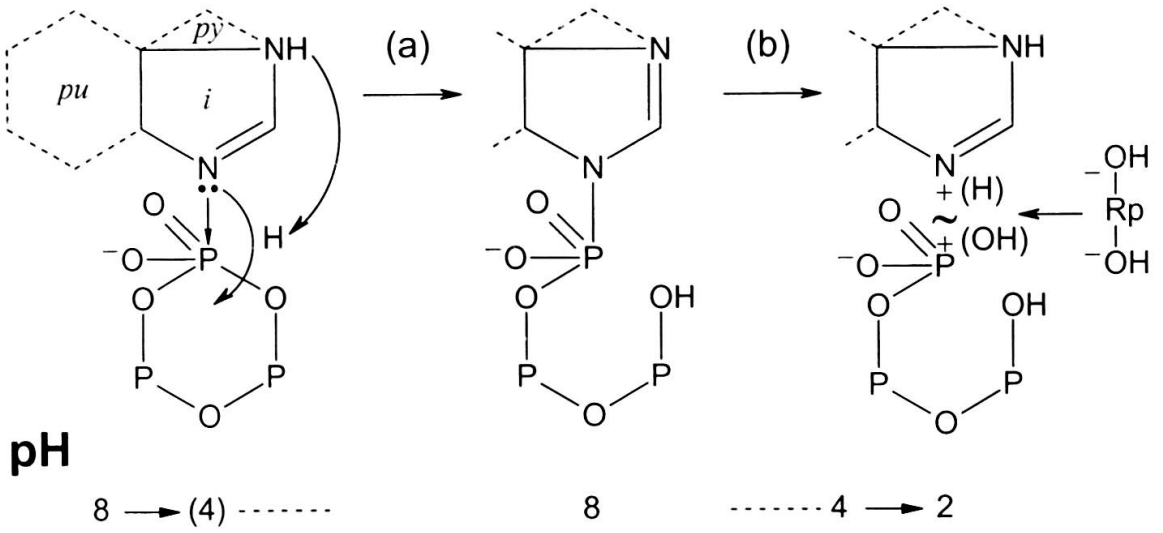


FIG. 1

Phosphoramide bonding of a nucleobase (*i*) triggered by Mg^{2+}-dependent (TURIAN & RIVARA-MINTEN, 2001) transient acidification – at least pH 4 for the *pKas* – inducing the prototropic "down tautomerization" of the base required to switch the nucleophilic attack of its ≥ N:— group on the electrophilic P atom of a thereby decyclized trimetaphosphate. The P~N bond is further stabilized by back "up tautomerization" of the nucleobase produced by environmental increase of the pH to at least 8 (a). The closed bond can only be reopened by (b) the secondary "down tautomerization" provoked by back acidification of the medium to pH 4 – 2, thereby allowing the insertion of ribose precursors (Rp).

3. 1C-5C ribosylation-bridging of opened phosphoramide bonds

The acid hydrolytic opening of the nucleobase-phosphate bond suggested us that it could provide molecular topology and energy powering for the intercalation of D-ribose precursors on the corner of each of their units, by N (1/9)-glycosyl ester bonding with the nucleobase, and phosphoester (5') bonding with the freed phosphate and thereby produce ribonucleotide monomers (TURIAN, 1997). However, ribose not being easily available because of its difficult synthesis its precursors 1C-3C might have been inserted before their further condensation into the pentose cycle, according to the autocatalytic reaction sequence proposed by MILLER (1998):

$$CH_2O + CH_2O \rightarrow \begin{matrix} CHO \\ | \\ CH_2OH \end{matrix} \qquad \begin{matrix} CH_2O \\ \rightarrow \end{matrix} \qquad \begin{matrix} CHO \\ CHOH \\ CH_2OH \end{matrix}$$

Formaldehyde 2C Glycolaldehyde + 3C Glyceraldehyde

= Pentose

All members of the polyol sequence could be detected in recent cosmochemical studies (see ORÓ, 2001). Its first member, 1C formaldehyde, is well-known for its oligomerization into formose and the production of a mixture of sugars but from which only low concentrations of D-ribose could be resolved (DECKER *et al.*, 1982, JOYCE, 1989, YUASA *et al.* 1995).

Another 1C compound, methylene glycol $CH_2(OH)_2$, is produced by hydrolysis from atmospheric CH_2O solubilized into rainwater and then present in the primitive ocean (KASTING & BROWN, 1998). In our hypothesis, the acid-induced opening by electric charge repulsion of the P+...+N bond of nucleobase-phosphate would make available the intrinsic high energy necessary for a first intermediate linking by such an dihydroxylated compound, providing the shorter bridge over the open P~N bond (Fig. 2) possibly then complexified into the 2C-4C precursors of D-ribose.

2C precursor glycolaldehyde, produced by polycondensation of formaldehyde, when further condensed by two (=4C) on the already phosphorylated 1C of methylene glycol, could close the pentose cycle of a ribonucleotide (Fig. 3). The role of 2C glycolaldehyde as dimerized product of CH_2O has been promoted by ESCHENMOSER (1995) and his team (MÜLLER *et al.*, 1990; PITSCH *et al.*, 1995) who studied the condensation of glycolaldehyde phosphate in the presence of a limited amount of formaldehyde and base (see SCHWARTZ, 1998). However, this biotic phosphorylation would require "modern" ATP, while cyclic triphosphate alone could have provided the prebiotic high energy required by the synthesis as shown by LOHRMANN (1977), ETAIX & ORGEL (1978, citing previous work by SCHWARTZ, 1969 and SAFFHILL, 1970) and as recently confirmed by ZUBAY & MUI (2001) who have phosphorylated ribonucleosides by trimetaphosphate. It remains to know whether the same phosphorylation could be successful with "preribonucleosides" such as adenine or cytosine-glyceraldehyde or the 3C precursor glyceraldehyde.

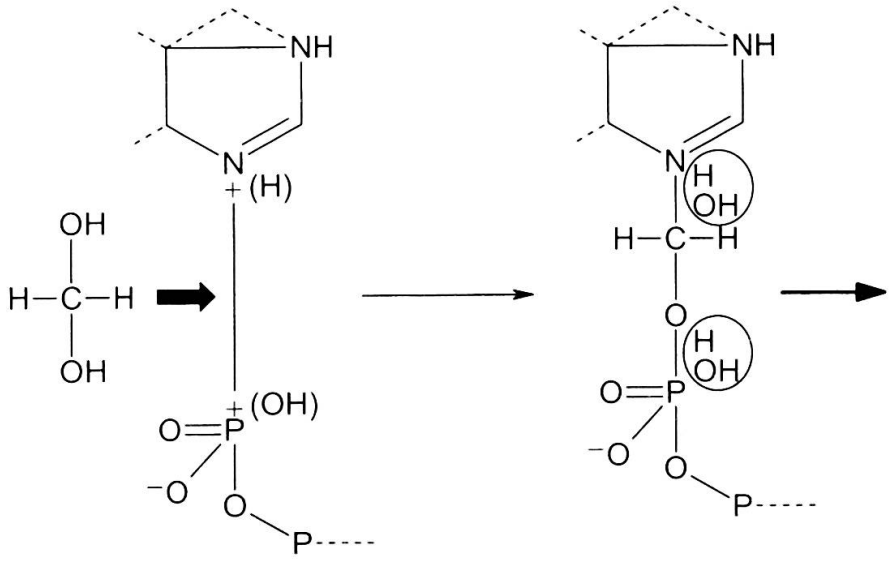


FIG. 2.

Opening of the nucleobase phosphoramide bond by the secondary acid-induced "down tautomerization" providing the opposite $N^+...{}^+P$ groups propitious to minimal bridging by the primal amphi-hydroxylated ribose precursor methylene glycol.

3C glyceraldehyde provides with its terminal C the phosphorylation site as 5C of ribose after its condensation with glycolaldehyde 2C thereby closing the pentose cycle (Fig. 3). Another 3C, glycerol, proposed to replace ribose in simpler informational molecules (SPACH, 1984) can be condensed with 1 CH_2O into the 4C of the acyclonucleoside (see JOYCE, 1989; ORGEL, 1992) or, possibly, with 2, thereby directly providing the 5C ribose.

5C ribose is directly involved in the synthesis of a ribonucleoside which could start from both its molecular extremities: from nucleobase ribosylated into nucleoside – a difficult process requiring heating (see FULLER *et al.*, 1972) – or from phosphate phosphorylating ribose into ribosephosphate (see BRACK, 1998). Ribose precursors such as glycolaldehyde-phosphate or glyceraldehyde-phosphate have been incriminated by KRISHNAMURTHY *et al.* (1986) and MOJZSIS *et al.* (1999) who have obtained an efficient phosphorylation of glycolaldehyde in dilute mineral solution. However, the secondary binding of these precursors with nucleobases remains uncertain. The reverse process of secondary phosphorylation – by trimetaphosphate rather than by the biotic ATP – of premade ribonucleosides has been obtained, as mentioned above. It then remains to know whether the same phosphorylation could be successful with "preribonucleosides" such as adenine or cytosine glycolaldehyde-glyceraldehyde.

The final synthesis of ribonucleotides could occur in a number of ways. According to the recent authoritative comments by JOYCE & ORGEL (1999) "the simplest, conceptually, would be to synthesize a nucleoside base, couple it to ribose, and finally phosphorylate the resulting nucleoside". Here, we propose a riboseless route such as that which involves intercalation of 1C – 3C ribose precursors between acid opened P~N

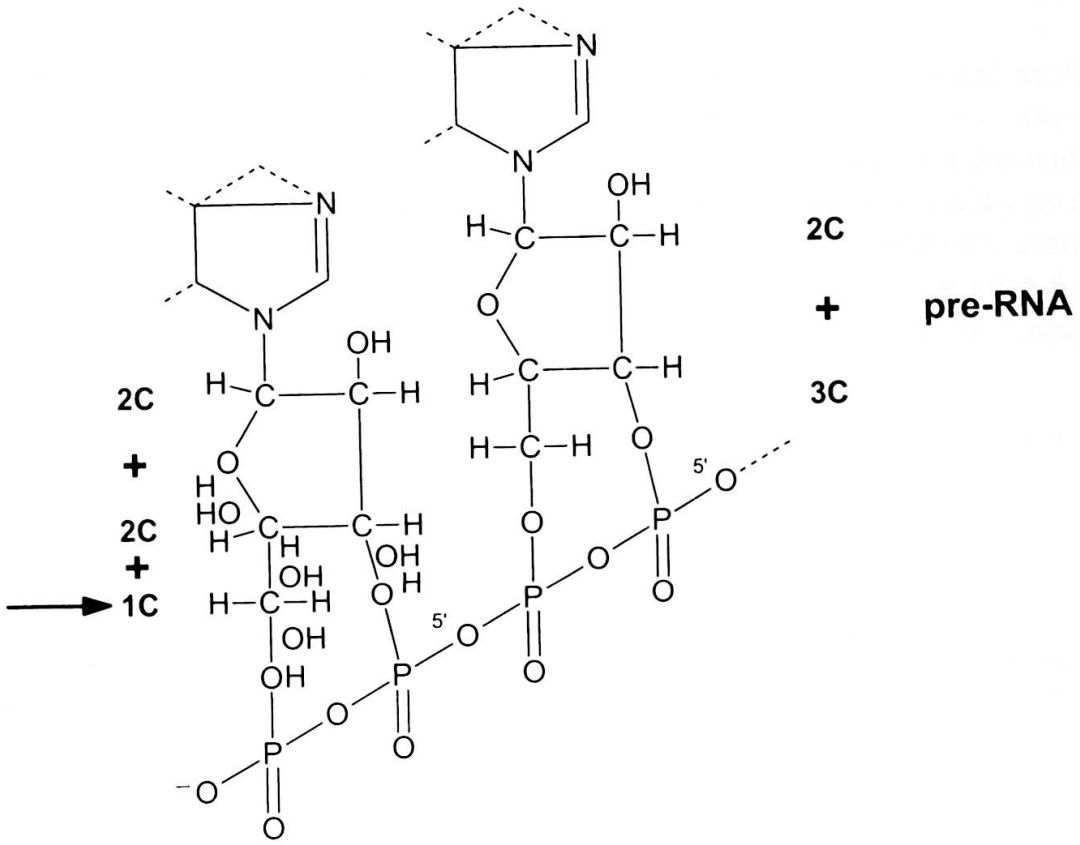


FIG. 3

Further bridging of the opened phosphoramide bond to complete the trimeric 5C ribonucleotide either by condensation of 1C with 2 x 2C glycolaldehyde (left) or only one 2C with 3C glycerol which directly provides the partner methyl C^1 bond to the P group (right).

bonding (Fig. 1) powered by the high energy released at the acid-induced opening of the bond and its further bridging electrically driven by the bilateral attraction of the $^-$charged hydroxyl groups of the C-precursors. These could follow the scale of increased complexity from 1C methylene glycol which forms the shortest bridge between a base and a phosphate group (Fig. 2). The trivalent monomer formed, i.e. nucleobase – 1C – phosphate, could be considered as the minimal protonucleotide, "robust" in acidic media by its N-C-P bonds (see page 3).

To fully enter into the "RNA world", the ribonucleotides, by either way produced have still to be assembled into polymers capable to replicate prebiotically (non enzymatically). For that, clay-type minerals have been found by ERTEM & FERRIS (1996) to catalyze the joining of imidazole-activated nucleotides. The oligonucleotides produced *in vitro* were pyro(di)phosphate linked (VISSCHER *et al.*, 1990; FERRIS, 1998).

Our modellized prenucleic phosphoramidates are also built on a repetitive diphosphate backbone (after splicing of 1P from the initial 3P monomer; see TURIAN & RIVARA-MINTEN, 2000) which should be maintained in the ribonucleotides produced after initial 1C → 5C = ribose insertion (Fig. 3). Full transition from pre-RNA to RNA would therefore require such a splicing process to insure the continuity of the phosphodiester bondings conferring increased stability to the finalized RNA strands.

CONCLUSIONS

According to Stanley Miller's group (LARRALDE *et al.*, 1995), the existence of a RNA-world implies either the difficult availability of a prebiotic source of ribose or the existence of RNA-like (pre-RNA) molecules with a different backbone. In such a "pre-RNA world", one solution could be peptide-nucleic acid (PNA) discovered in 1993 by NIELSEN, as recorded by LAHAV (1999).

In their brilliant "Spark of Life", WILLS & BADA (2000) raised the question "Is the phosphate in the nucleic acid backbone really necessary?", followed by the pertinent remark that the PNA might well be "only one of many possible molecules that served in the pre-RNA world." Our proposal that the polynucleobasephosphate could function as another pre-RNA positively answers both the questions and the remark.

Most significant in the further transition from this new type of pre-RNA to RNA must have been their differential pH-sensitivity which could have been modulated by the prevention of the acidic tautomerization of nucleobases by their progressive ribosylation (see § 2), thereby providing the necessary wider-range pH stability of nucleotides securing the coding accuracy of the RNA world.

RÉSUMÉ

Phosphoramidates prénucléiques dans la transition pré-ARN-ARN ? Les bases nucléiques peuvent être phosphoramido-liées en infopolymères nucléiques. L'ouverture acido-induite de leur liaison énergétique par tautomérisation prototropique sépare les groupes répulsifs $N^{+}...{}^{+}P$ lesquels pourraient être pontés par des précurseurs 1C – 3C du ribose, bihydroxylés et négativement chargés.

Mots-clés: phosphoramide, prénucléique, nucléobases, ouverture acido-induite, cycle trimétaphosphate.

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