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An ab initio computational study of thiamin synthesis from gaseous reactants of the interstellar medium

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Abstract

A set of chemical reactions is proposed to account for the formation of thiamin derivatives from gaseous reactants that have been identified in the interstellar medium, and may have been relevant to a prebiotic atmosphere. The gaseous mixture consisted of methanimine, acetonitrile, cyanoacetylene, ammonia, acetylene, allylene, hydrogen sulfide, thioformaldehyde, and hydrogen in the presence of water. Most of the reactions appear to be exothermic.

The reactions have been shown to be feasible from the overall enthalpy changes in the ZKE approximation at the HF and MP2/6-31G* level.

Keywords: Thiamin; Methanimine; Cyanoacetylene; Acetonitrile; Allylene; Acetylene; Ammonia

1. Introduction

Thiamin, vitamin B1, is the original dietary factor for which Funk coined the designation "vitamin" in 1911 [1]. About 1.5 mg is required by man daily [2]. This nutritional factor required by all living cells [3] prevents and reverses the deficiency disease beri-beri in man and polyneuritis in birds. The biological significance of vitamin B1 lies in the fact that its pyrophosphoric ester is the prosthetic group of the enzyme carboxylase [4]. Thiamin pyrophosphate serves as the coenzyme for two classes of enzyme-catalyzed reactions in the mainstream of carbohydrate metabolism in which the aldehyde groups are removed and/or transferred: the decarboxylation of α-keto acids, and also the formation or degradation of α-ketols. In these reactions the thiamin pyrophosphate serves as a transient carrier of a covalently bound "active" aldehyde group. Mg^+ is also required as a cofactor [5].

Thiamin consists of a substituted pyrimidine joined by a methylene bridge to a substituted thiazole, Fig. 1. Synthetic thiazolium salts are able to catalyse the same types of enzymic reactions. The same mechanism is thought to be followed by both enzymic and non-enzymic reactions [6]. B1 is a chemical chameleon [7], whose deceptively simple structure changes with pH. It readily undergoes deprotonation of the 2 position of the thiazolium ring to give an ylide; the reaction of considerable biological importance.

Biosynthesis of thiamin occurs in most microorganisms and higher plants, but there are chemically distinct routes. For anaerobic bacteria the precursors of the pyrimidine unit are glycine, formate and glutamine [2]: in *Escherichia coli* the thiazole unit is formed from tyrosine, cysteine and deoxyxylulose-5-phosphate [8]. The thiazole is then coupled with the pyrimidine pyrophosphate. A final phosphorylation gives thiamin pyrophosphate.

This paper is the first to suggest a route to thiamin synthesis based on spontaneous gaseous reactions in the presence of water. Although geological records of conditions in the atmosphere and hydrosphere of the early Earth are almost completely lacking [9,10], the molecules: methanimine, acetonitrile, cyanoacetylene, allylene, and acetylene have long been identified in the interstellar medium [11,12], and should give a large range of organic compounds. For this work the assumption is also made that some of the components that are presently found on Titan [12,13] are also present, particularly cyanoacetylene, and a study of its photochemistry indicated that

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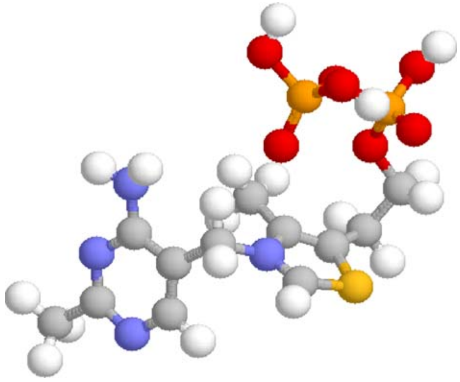


Fig. 1. The structure of thiamin (Vitamin B1) in a preferred conformation.

diacetylene can be produced [14,15] by a free radical reaction. The source of the sulfur is here taken to be hydrogen sulfide and thioformaldehyde.

The question being posed is whether the complex vitamin B1 structure was available from a prebiotic atmosphere or was this compound produced by cells during biochemical evolution?

If a set of chemical reactions can be deduced for the spontaneous formation of thiamin from molecules reasonably expected to be present in a prebiotic atmosphere, then the question is at least open; apart from depicting a very useful synthesis of thiamin. However, for a minor compound to be produced in a small quantity at least one of the steps in the synthesis is expected to be only marginally favourable.

In this paper the primary sources for the carbon, nitrogen, and hydrogen found in thiamin and thiamin derivatives are therefore taken to be molecules long identified in the interstellar medium, along with ammonia, thioformaldehyde and hydrogen. This does not exclude any precursors of these molecules or some derivatives. An examination of the total energy of these molecules and their transformation products; 5-methene-2-methyl-pyrimidine-4-one, and 4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole ion, suggests that thiamin could have arisen from reactions originating in the gas phase.

For the spontaneous chemical formation of these biologically important molecules it is satisfying if all are formed from the same initial milieu of reactants by established chemical reactions that are kinetically feasible and preferably thermodynamically favoured.

Here, one such set of reactions is proposed based on the availability of the primary reactants and thermodynamic considerations.

2. Computational methods

The computations tabulated in this paper used the SPARTAN [16] and GAUSSIAN98 [17] commercial packages, using IBM RISC 6000 and SP2 computers. These computer programs provide a solution to the quantum mechanical Schrodinger equation [18] for a many-electron molecule in terms of the energy states and corresponding wave functions of the molecule. To provide practical methods for the solution of this equation commercial programs use the Hartree–Fock Approximation which separates the wave function into a product of one-electron wave functions, giving rise to a set of coupled differential equations (the Hartree–Fock equations), each involving a single electron. It has become standard to represent the results from this calculation in the designation, HF/6-31G*, to indicate that the energy is from a Hartree–Fock calculation and that a particular set of Gaussians (6-31G*) has been used to represent the atomic orbitals. This designation is used in this paper.

The Hartree–Fock model treats the motion of individual electrons as weakly dependent on one another, whereas a calculation of the correlation of the motion of electrons can lead to a decrease of electron–electron repulsive energy, and a lowering of the overall energy. The method of Moller–Plesset [19] is perhaps the simplest model which improves on Hartree–Fock theory by incorporating electron correlation. In this paper, calculations designated, MP2/6-31G*, indicate a second-order Moller–Plesset calculation using the basis set 6-31G*. The calculations refer to the isolated molecule in the gas phase.

Once the total energies of all the molecules have been calculated near the absolute zero, a comparison is made of the combined energy of the reactants versus the combined energy of the products. If the combined energy of the products is less than the combined energy of the reactants it may show that the reaction is also likely to be spontaneous at higher temperatures.

Equilibrium structures were calculated at the HF/6-31G* and MP2/6-31G* level. For the large thiazole ions energies to a higher accuracy than MP2 are not available. For jobs run under GAUSSIAN98, geometry optimizations used the VTIGHT option.

The basis set used in the MP2 geometry optimizations was the standard split-valence double zeta basis set, augmented with a d-type polarization function on the non-hydrogen atoms [20].

The lowest ab initio level of theory which provides an account of the dispersion forces and correlation correction to the dipole moment is the MP2 level (the second order Moller–Plesset perturbation theory). This is a suitable level of theory for the systems considered in the present work, and this model may show smaller uncertainties than those from density functional theory [21], although the cost is higher for the larger molecules.

Since calculated Hartree–Fock vibrational frequencies tend to exceed known experimental values, the calculated frequencies were scaled by a factor of 0.89, when used to derive zero point vibrational energies (ZPE) and thermochemical corrections to the total energies. This is consistent with the recommendation of Pople et al. [22]. The zero-point energies were only calculated at the HF level of accuracy and have an error of ±0.008 h. Calculations that are only at the HF level of accuracy are specifically indicated as, $\Delta H_{(\mathrm{HF})}$. The potential energy scans allowed all the internal coordinates to vary except the two that were constrained to produce the two-dimensional plots shown. However, transition structures calculated using Hartree–Fock methods may differ from those using larger basis sets or including correlation [18]. Most of the atmospheric gaseous reactions considered would be presumed to be able to access considerable activation energy from photochemical excitation [23]. Calculations throughout this paper use the atomic unit of energy [18]: 1 h=4.3597482×10^{-18} J [17]. Activation energies are also given in kilojoules per mole.

3. Results and discussion

3.1. Total energies (hartrees)

The total energies and zero point energies for the HF and MP2/6-31G* equilibrium geometries are given in Tables 1 to 3.

3.2. The formation of initial reactants

For the overall reaction to form thiamin it is desirable to justify the presence of initial reactants.

The method to produce the pyrimidine moiety requires the initial presence of acetonitrile, methanimine and cyanoacetylene [11,12].

For the formation of the thiazole moiety pent-1,3-diyne, ammonia and thioformaldehyde are required.

Here, some justification for the initial presence of these compounds in a possible prebiotic atmosphere is presented.

3.2.1. The formation of thioformaldehyde

The presence of some hydrogen sulfide is expected to exist from the hydrogenation of sulfur and the hydrolysis of ammonium sulfide. Thioformaldehyde could arise from an exchange with formaldehyde according to the energetically favourable equation:

$$CH_2{=}O + H_2S \rightarrow CH_2{=}S + H_2O$$

$$\Delta H = -0.33458\text{h}$$

or via free radical mechanisms.

3.3. The formation of 4-imido-5-methene-2-methyl-pyrimidine

As proposed here the thiamin structure is derived from two moieties that are formed first, namely, 4-imido-5-methene-2-methyl-pyrimidine, and 4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole ion. The formation of each of these is considered separately. The activation energies for the molecules are evaluated at the HF level of accuracy. The data relevant to these calculations is given in Table 3.

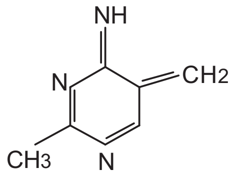
Table 1
HF and MP2/6-31G* total energies and zero point energies (hartrees) for the respective equilibrium geometries

Molecule	HF hartree	MP2 hartree	ZPE (HF) hartree
acetylene	−76.81783	−77.06679	0.02945
allylene	−115.86432	−116.24181	0.06010
cyanoacetylene	−168.54943	−169.07910	0.02989
prop-2-yne imine	−169.70389	−170.23556	0.05475
$CH_2{=}S$	−436.50646	−436.75511	0.02389
CH_3CN	−131.91275	−132.3454	0.04563
pyrophosphoric acid	−1208.01709	−1209.48686	0.08180
H_2O	−76.01075	−76.19924	0.02148
CO	−112.73434	−113.02818	0.02431
NH_3	−56.18436	−56.35738	0.03529
H_2	−1.12683	−1.14414	0.01034
H_2S	−398.31094	−398.43613	0.01127
OH^-	−75.32660		

Table 2
HF and MP2/6-31G* total energies and zero point energies (hartrees) for the respective equilibrium geometries

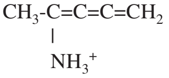
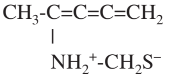
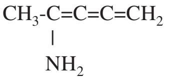
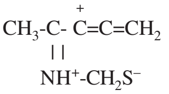
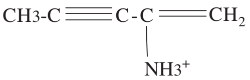
Molecule	HF hartree	MP2 hartree	ZPE (HF) hartree
pent-1,3-diyne	−191.54560	−192.16934	0.06933
5-methene-2-methyl-pyrimidine-4-one	−414.43649	−415.67414	0.12245
4-imido-5-methene–2-methyl-pyrimidine	−394.59093	−395.81048	0.13559
4-methyl-5-(1,2-ethandienyl)-3-thiazolinium ion	−683.55062	−684.57977	0.13827
4-methyl-5-(ethan-1-ene-2-pyro phosphoryl)-3-thiazolinium ion	−1891.64567	−1894.14366	0.22619
4-methyl-5-(2-pyrophosphoryl ethanyl)-thiazole ion	−1891.65622	−1894.17739	0.22670
thiamin	−2286.28539	−2290.08819	0.36652
4-imido-5,6-cyclo-propanyl-2-methyl-pyrimidine	−394.51517		

3.3.1. The formation of 4-imido-5-methene-2-methyl-pyrimidine from methanimine, acetonitrile and cyanoacetylene



4-imido-5-methene-2-methyl-pyrimidine

Table 3
HF and MP2/6-31G* total energies and zero point energies (hartrees) for the respective equilibrium geometries

Molecule	HF hartree	MP2 hartree	ZPE (HF) hartree
N-methenyl acetamidine	−225.95853	−226.65934	
N-methenyl acetamidinyl cyanoacetylene	−394.51517	−395.74482	
$CH_3{-}C{=}C{=}C{=}CH_2^+$	−191.86529	−192.46847	
 $CH_3\text{-}\underset{NH_3^+}{\underset{\mid}{C}}{=}C{=}C{=}CH_2$	−248.11762		0.12982
 $CH_3\text{-}\underset{NH_2^+\text{-}CH_2S^-}{\underset{\mid}{C}}{=}C{=}C{=}CH_2$	−684.24853	−685.29706	0.14958
 $CH_3\text{-}\underset{NH_2}{\underset{\mid}{C}}{=}C{=}C{=}CH_2$	−247.76127	−248.57903	0.11448
 $CH_3\text{-}\underset{NH^+\text{-}CH_2S^-}{\underset{\mid\mid}{C}}\text{-}\overset{+}{C}{=}C{=}CH_2$	−683.43871	−684.49017	0.13257
 $CH_3\text{-}C\equiv C\text{-}\underset{NH_3^+}{\underset{\mid}{C}}{=}CH_2$	−248.13804		0.13075

The overall stoichiometry is as follows:

$$HC{\equiv}CH + CO + 2NH_3 + HC{\equiv}C{-}CN \rightarrow C_6H_7N_3 + H_2O$$

$$\Delta H = -0.10105\text{h}$$

Without the imidolysis the reaction is favourable:

$$HC{\equiv}CH + CO + NH_3 + HC{\equiv}C{-}CN \rightarrow C_6H_6N_2O$$

$$\Delta H = -0.12222\text{h}$$

The imidolysis is not favourable but is kinetically feasible if the activation energy is not much greater than the enthalpy of reaction [24].

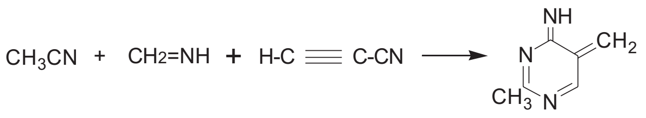
$$C_6H_6N_2O + NH_3 \rightarrow C_6H_7N_3 + H_2O$$

$$\Delta H = 0.02118\text{h}$$

The overall enthalpy change is favourable.

This reaction is energetically viable, but the mechanism is far from clear. Here a choice is made for the mechanism only to show that at least one route between reactants and products is possible, and the activation energy is not prohibitive. However, for these gaseous reactions at least one of the steps is expected to be rate limiting.

3.3.1.1. The formation of the pyrimidine ring. The pyrimidine ring is considered to be formed from the progressive nucleophilic condensation of methanimine with acetonitrile, and of the product with cyanoacetylene.



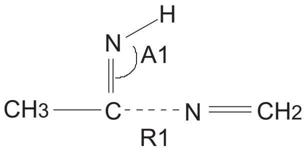
$\Delta H = -0.05584\text{h}$.

3.3.1.2. The formation of methanimine-acetonitrile adduct (N-methenyl acetamidine). The condensation of methanimine with acetonitrile is exothermic.

$$CH_2{=}HN + CH_3CN \rightarrow CH_2{=}N{-}C({=}NH){-}CH_3$$

$$\Delta H_{(HF)} = -0.00373\text{h}$$

The potential energy diagram is given in Fig. 2.



The activation energy to form *N*-methenyl acetamidine from methanimine and acetonitrile was calculated as, 0.0717 h (188 kJ mol^{-1}), whereas the activation energy to form the transition state from *N*-methenyl acetamidine was found to be, 0.0755 h (198 kJ mol^{-1}). The molecules may achieve considerable excitation from ultraviolet absorption as for compounds containing double bonds [23].

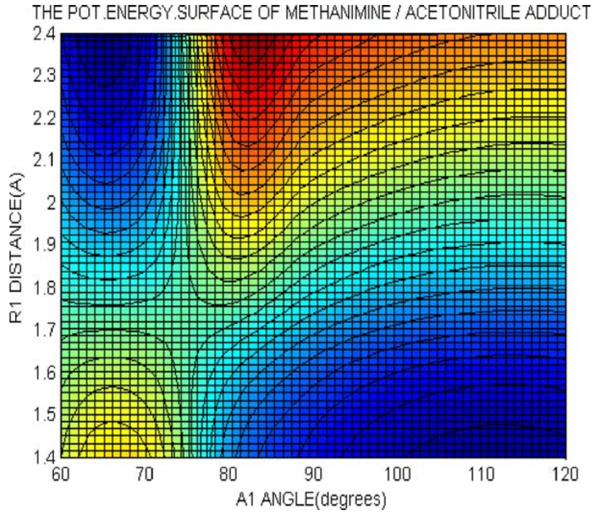
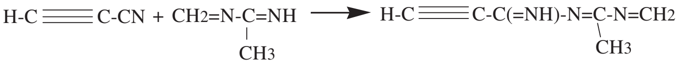


Fig. 2. The potential energy surface for the conversion of methanimine and acetonitrile to *N*-methenyl acetamidine. The minimum of the *N*-methenyl acetamidine is at (A1 = 110, R1 = 1.4). The minimum for acetonitrile is at (A1 = 65, R1 = 2.4). The saddle point is at (A1 = 75, R1 = 1.7).

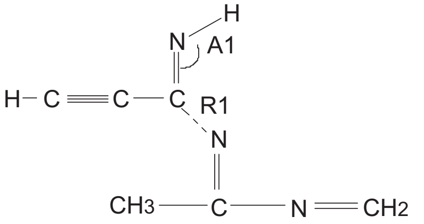
3.3.1.3. The formation of N-methenyl acetamidinyl cyanoacetylene adduct. The condensation of cyanoacetylene with *N*-methenyl acetamidine is also exothermic.



$$H{-}C{\equiv}C{-}CN + CH_2{=}N{-}\underset{\displaystyle CH_3}{C}{=}NH \longrightarrow H{-}C{\equiv}C{-}C({=}NH){-}N{=}\underset{\displaystyle CH_3}{C}{-}N{=}CH_2$$

$\Delta H_{(HF)} = -0.00722\text{h}$.

The potential energy surface is given in Fig. 3.



The activation energy to form the transition state from *N*-methenyl acetamidinyl cyanoacetylene, shown in Fig. 3 was calculated at the HF level as, 0.0331 h (87 kJ mol^{-1}), whilst the formation from the *N*-methenyl acetamidine plus cyanoacetylene was, 0.0403 h (106 kJ mol^{-1}). Again, photochemical excitation would be expected to be available to activate the molecules.

3.3.1.4. The formation of 4-imido-5-methene-2-methyl pyrimidine. It is expected that the methylene hydrogen of 4-imido-5-methene-2-methyl pyrimidine, in which the methylene hydrogen acts as a nucleophile, will form a hydrogen bond complex with a T-structure with the acetylenic group [25]. The hydrogen

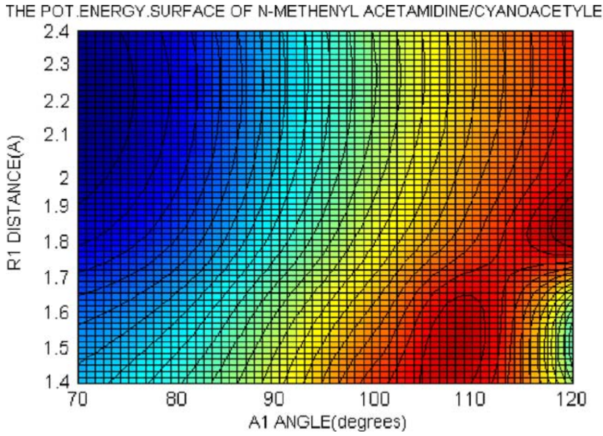
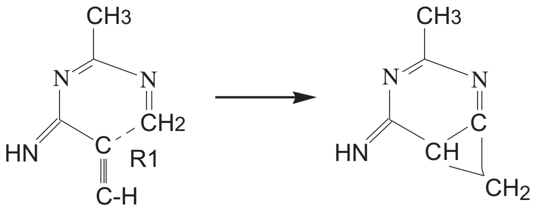


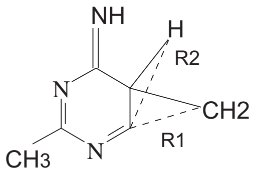
Fig. 3. The potential energy surface for the conversion of *N*-methenyl acetamidine and cyanoacetylene to form *N*-methenyl acetamidinyl cyanoacetylene. The minimum of the *N*-methenyl acetamidinyl cyanoacetylene is at (A1 = 120, R1 = 1.5). The minimum for the *N*-methenyl acetamidine plus cyanoacetylene is at (A1 = 70, R1 = 2.4). The saddle point is at (A1 = 115, R1 = 1.7).

may also be reactive enough to add across the acetylenic bond [26], with variable regioselectivity and low activation energy [27].

When an optimization of *N*-methenyl acetamidinyl cyanoacetylene was attempted the formation of the pyrimidine ring was always spontaneous without any activation energy, with the formation of a three-membered ring, as shown,



However, this compound with the cyclopropanyl ring is not the lowest energy isomer, but may be a reactive intermediate in the synthesis of thiamin. The open-chain structure is lower in energy, and may be achieved with the variation of a number of internal coordinates. For example, with the stretches shown, the potential energy diagram in Fig. 4, is achieved, and the three-membered ring dissociates.



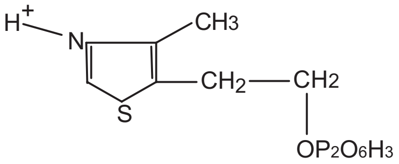
The enthalpy change to produce the open-chain structure is,

$$\Delta H_{(\mathrm{HF})} = -0.07576\mathrm{h}$$

The activation energy for open-chain formation was calculated as 0.1198 h (315 kJ mol^{-1}), whereas the activation energy to close the three-membered ring was 0.1955 h (513 kJ mol^{-1}).

It does seem reasonable to assume that with such a large number of compounds potentially in the gaseous phase that more than one mechanism may often be relevant even if some of the chemical species are not present in great concentration.

3.4. The formation of 4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole ion



4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole

The overall stoichiometry to form the thiazole moiety is as follows, and the enthalpy change is favourable:

$$\mathrm{HC{\equiv}CH} + \mathrm{CH_3{-}C{\equiv}CH} + \mathrm{NH_3} + \mathrm{H_4P_2O_7} + \mathrm{CH_2} = \mathrm{S} + \mathrm{H^+} \rightarrow \mathrm{C_6H_{12}NO_7P_2S^+} + 2\mathrm{H_2}$$

$$\Delta H = -0.54536\mathrm{h}$$

The formation of the thiazole is postulated here to proceed via pent-1,3-diyne, formed as follows.

3.4.1. The formation of 4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole ion from pent-1,3-diyne

3.4.1.1. The formation of pent-1,3-diyne. The presence of acetylene and allylene should lead to the following reaction from photolysis of these molecules [14]:

$$\mathrm{HC{\equiv}CH} + \mathrm{CH_3{-}C{\equiv}CH} \rightarrow \mathrm{CH_3{-}C{\equiv}C{-}C{\equiv}CH} + \mathrm{H_2}$$

$$\Delta H = -0.01366\mathrm{h}$$

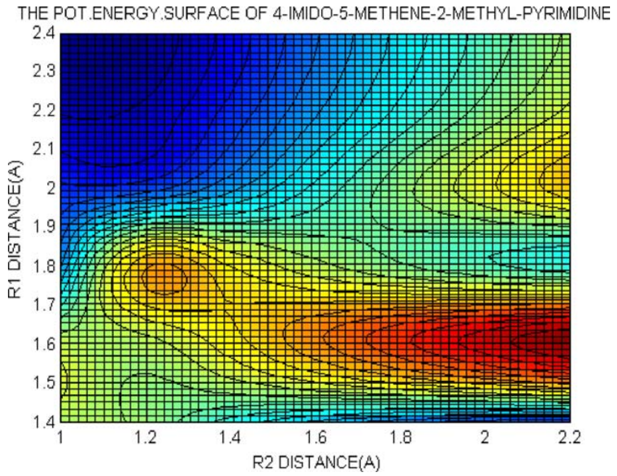
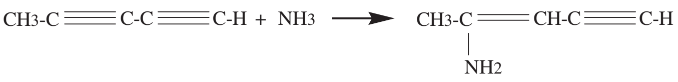


Fig. 4. The potential energy surface for the conversion of 4-imido-5, 6-cyclopropanyl-2-methyl-pyrimidine to the open-chain, 4-imido-5-methene-2-methyl-pyrimidine. The minimum of the 4-imido-5,6-cyclopropanyl-2-methyl-pyrimidine is at (R1 = 1.4, R2 = 1.6). The minimum for the 4-imido-5-methene-2-methyl-pyrimidine is at (R1 = 2.4, R2 = 1.0). The saddle point is at (R1 = 1.5, R2 = 1.1).

3.4.1.2. The formation of pent-4-amino-1,2,3-triene. The general reaction of an yne with ammonia is here depicted using pent-1,3-diyne.



$$CH_3\text{-}C\equiv C\text{-}C\equiv C\text{-}H + NH_3 \longrightarrow CH_3\text{-}\underset{\displaystyle NH_2}{\underset{|}{C}}=CH\text{-}C\equiv C\text{-}H$$

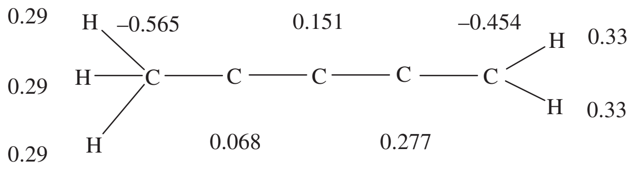
$$\Delta H_{(HF)} = -0.06475\text{h}$$

The suggested reaction mechanism for this as described here is the protonation of the pent-1,3-diyne to form a linear protonated molecule. This could occur in solution or with the hydronium ion [28].

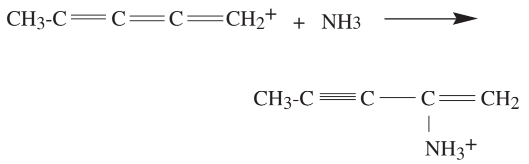
$$CH_3\text{-}C\equiv C\text{-}C\equiv C\text{-}H + H^{+} \longrightarrow CH_3\text{-}C=C=C=CH_2^{+}$$

$$\Delta H_{(HF)} = -0.3196941\text{h}$$

This may subsequently add ammonia. This reaction can occur at both the 2 and 4 carbon atoms, and both reactions would be expected to occur from the formal charges present on the protonated pent-1,3-diyne. These are shown as,



Two stable molecules may be formed on reaction with ammonia, the 2-amino-pent-1ene-3yne^{+} and 4-amino pent-1,2,3-triene^{+}. The enthalpy change for the reaction to form the 2-amino-pent-1ene-3yne^{+} is as shown.

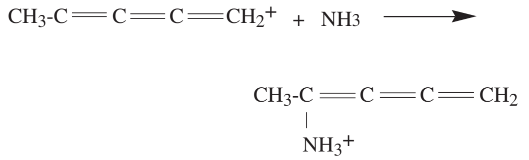


$$CH_3\text{-}C=C=C=CH_2^{+} + NH_3 \longrightarrow CH_3\text{-}C\equiv C-\underset{\displaystyle NH_3^{+}}{\underset{|}{C}}=CH_2$$

where,

$$\Delta H_{(HF)} = -0.088383\text{h}$$

The molecule that is required for the synthesis is the 4-amino pent-1,2,3-triene, as shown.

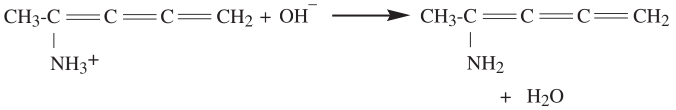


$$CH_3\text{-}C=C=C=CH_2^{+} + NH_3 \longrightarrow CH_3\text{-}\underset{\displaystyle NH_3^{+}}{\underset{|}{C}}=C=C=CH_2$$

where,

$$\Delta H_{(HF)} = -0.0679674\text{h}.$$

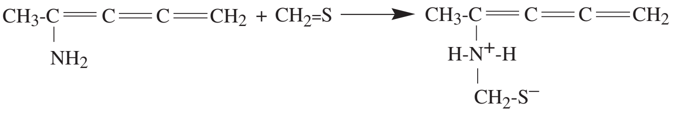
3.4.1.3. The formation of 4-(thiol-methylamino)-pent-1,2,3-triene. Although the protonated 4-amino-pent-1,2,3-triene could react with thioformaldehyde by a transfer reaction, it is convenient to consider the reaction of the neutral molecule formed by reaction with the alkaline medium.



$$CH_3\text{-}\underset{\displaystyle NH_3^{+}}{\underset{|}{C}}=C=C=CH_2 + OH^{-} \longrightarrow CH_3\text{-}\underset{\displaystyle NH_2}{\underset{|}{C}}=C=C=CH_2 + H_2O$$

$$\Delta H_{(HF)} = -0.32780\text{h}$$

This amino compound can be expected to react with thioformaldehyde [29], according to the following equation to give a zwitterion, as shown,

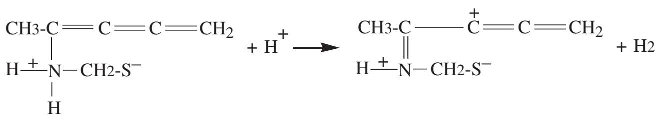


$$CH_3\text{-}\underset{\displaystyle NH_2}{\underset{|}{C}}=C=C=CH_2 + CH_2{=}S \longrightarrow CH_3\text{-}\underset{\displaystyle \underset{\displaystyle CH_2\text{-}S^{-}}{\underset{|}{H\text{-}N^{+}\text{-}H}}}{\underset{|}{C}}=C=C=CH_2$$

$$\Delta H = 0.02356\text{h}$$

This reaction involves just the approach of the two molecules along a reaction coordinate with an activation energy of just, 0.02203 h (59 kJ mol^{-1}), to form the stable activation state which is the zwitterion ion. The activation energy to dissociate this complex was calculated as just, 0.00342 h (9 kJ mol^{-1}).

3.4.1.4. The formation of 4-(thiol-methylimino)-pent-1,2,3-triene. The 4-(thiol-methylamino)-pent-1,2,3-triene may undergo a very exothermic reaction with a hydrogen anion acceptor, here depicted as a hydrogen ion, to produce an adduct having a positive charge. The most favourable sequence for this to occur is prior to ring closure.

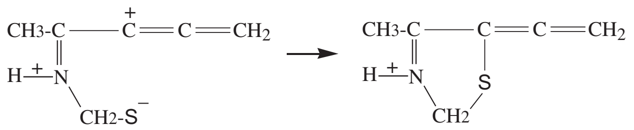


$$CH_3\text{-}\underset{\displaystyle \underset{\displaystyle H}{\underset{|}{H\overset{+}{-}N-CH_2\text{-}S^{-}}}}{\underset{|}{C}}=C=C=CH_2 + H^{+} \longrightarrow CH_3\text{-}\underset{\displaystyle H\overset{+}{-}N-CH_2\text{-}S^{-}}{\underset{\|}{C}}-\overset{+}{C}=C=CH_2 + H_2$$

$$\Delta H = -0.32980\text{h}$$

This highly favourable reaction should not require any significant activation energy as it only involves the approach of a proton. The sulphur–nitrogen bond length was calculated as 1.83 A.

3.4.1.5. The formation of 4-methyl-5(1,2-ethanedienyl)-3-thiazoline ion. The formation of 4-methyl-5(1,2-ethanedienyl)-3-thiazoline ion just involves the closure of the ring, during which the extended form of the molecule becomes more compact, and finally a stable thiazole molecule is formed, as shown.



$$\Delta H = -0.09792\text{h}$$

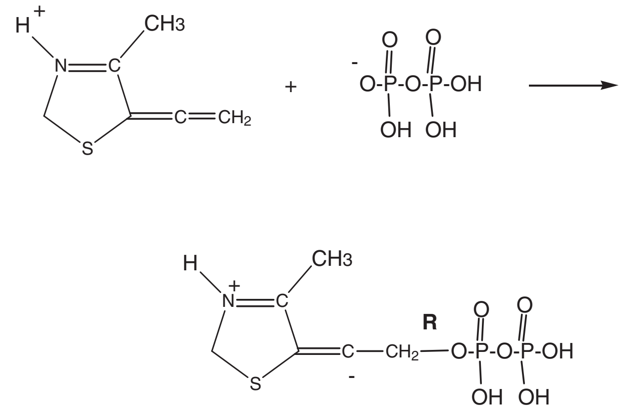
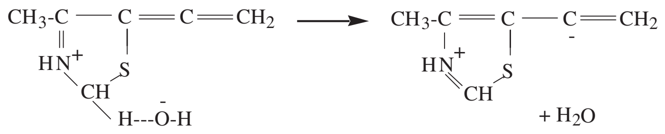


Fig. 5. The transition state for the extension of the C–O (*R*) bond. *R* is the reaction coordinate.

This only involves the acquisition of sufficient activation energy for the system of conjugated double bonds to be approached. To form the ring the activation energy was calculated as, 0.07225 h (190 kJ mol^{-1}), whilst the activation energy to break the ring open was found to be, 0.18630 h (489 kJ mol^{-1}).

3.4.1.6. The formation of 4-methyl-5(1,2-ethanedienyl)-3-thiazole ion. The formation of the thiazolinium ion involves the abstraction of a proton from the methylene group bonded to the sulfur atom. This was simulated as the approach of a hydroxyl ion to the vicinity of one of the methylene hydrogens, followed by an elongation of the C–H bond, as shown,



$\Delta H_{(\mathrm{HF})} = -0.22607\mathrm{h}$

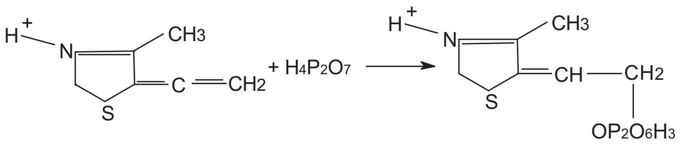
The reaction was spontaneous without any recorded activation energy as the C–H bond was elongated.

3.4.2. The formation of 4-methyl-5-(2-pyrophosphoryl-ethenyl)-3-thiazolinium ion

A compound as reactive as an allene may be able to condense with pyrophosphoric acid or other phosphorous acids in an equation as shown:

$C_6H_8NS^+ + H_4P_2O_7 \rightarrow C_6H_{12}NO_7P_2S^+$

$\Delta H = -0.07159\mathrm{h}$



4-methyl-5-(1,2-ethandienyl)-3-thiazolinium ion

4-methyl-5-(2-pyrophosphoryl-ethenyl)-3-thiazolinium ion

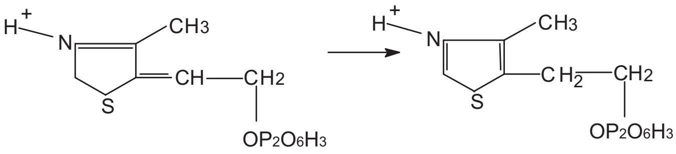
The activation energy for this reaction was estimated by extending the C–O bond of the product with the molecule having zero net charge, as shown below in Fig. 5.

The activation energy for bond breaking of the neutral product was just 0.00696 h (18 kJ mol^{-1}). However, the neutral product becomes much more stable on protonation, when its total energy drops appreciably.

The activation energy to form the bond was found to be 0.05116 h (134 kJ mol^{-1}).

3.4.3. The formation of 4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole ion

A prototropic shift is favourable to give the final thiazole moiety.



4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole

$\Delta H = -0.03327\mathrm{h}$

3.5. The overall energy for the formation of thiamin

These two moieties may combine with a very small negative energy change to give thiamin pyrophosphate as shown in Fig. 6.

$\Delta H = -0.09655$ h.

The activation energy for this reaction was found by calculating the activation energy to break the bond as depicted below in Fig. 7.

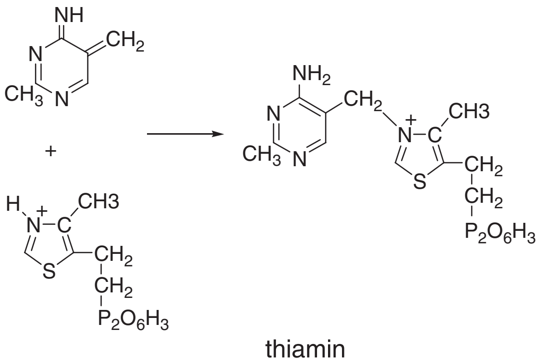


Fig. 6. The formation of thiamin from 4-imido-5-methene-2-methyl-pyrimidine and 4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole ion.

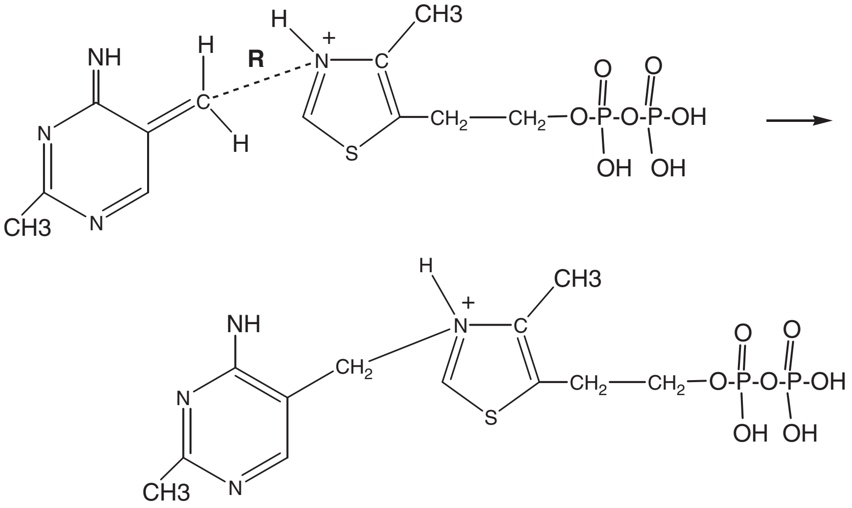


Fig. 7. Transition state for the formation of thiamine from the pyrimidine and thiazole entities along the N–C (*R*) bond. *R* is the reaction coordinate.

The activation energy for bond formation was found to be essentially zero with the reactants being higher in energy than the transition state.

The activation energy for bond breaking was found to be very small, 0.02227 h (59 kJ mol^{-1}).

4. Conclusion

The exact sequence of reactions leading to either the 5-methene-2-methyl-pyrimidine-4-one moiety or the 4-methyl-5-(2-pyrophosphoryl-ethanyl)-thiazole ion moiety is open to conjecture. Here, the only reaction that is not exothermic is the formation of the amino–thioformaldehyde adduct, which might be considered a transient transition state. This is a classical organic reaction which should be easily attainable from photochemical excitation of either reactant, or both. Most of the activation energies in the sequence of reactions would appear to be attainable by the same method.

Whilst many sequences of reactions may be engendered for the synthesis of thiamine, there is no reason to suppose that nature would not have used readily available reactants in reactions that at least at low temperatures are calculated as thermodynamically and kinetically viable.

From the postulates presented here it is clear that prebiotic paths to the biologically active molecules are kinetically accessible, if not unique. Further work at a higher level of accuracy may result in a correction to the enthalpies calculated here.

Acknowledgements

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