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A plausible prebiotic synthesis of pyridoxal phosphate: Vitamin B_6 – A computational study

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Abstract

A set of chemical reactions is proposed to account for the formation of pyridoxal phosphate, Vitamin B_6, from a primeval atmosphere composed of cyanoacetylene, diacetylene, carbon monoxide, hydrogen, water, and a phosphoric acid. 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.

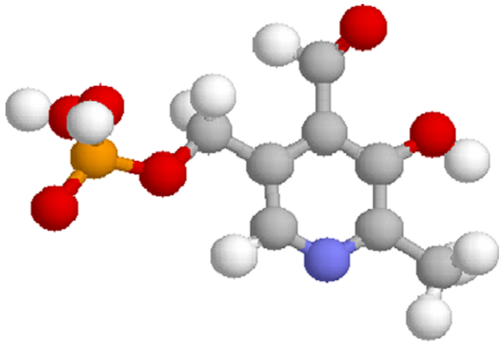
Keywords: Pyridoxal phosphate; Cyanoacetylene; Diacetylene; Carbon monoxide; Hydrogen; Water; Phosphoric acid

1. Introduction

Pyridoxal phosphate is a biologically active form of Vitamin B_6, Fig. 1, first identified as essential in the nutrition of the rat to prevent dermatitis [1,2]. The pyridoxal phosphate coenzymes are extremely versatile, functioning in a large number of different enzymatic reactions in which amino acids or amino groups are transformed or transferred.

The most common type of enzymatic reaction requiring pyridoxal phosphate as coenzyme is transamination, the transfer of the α-amino group of an amino acid to the α-carbon of an α-keto acid. In the catabolism of at least 12 of the amino acids the α-amino group is enzymatically removed by transamination. The pyridoxal phosphate functions as a coenzyme by virtue of the ability of its aldehyde group to react with the α-amino group of the amino acid substrate to yield a Schiff's base between the enzyme-bound pyridoxal phosphate and the amino acid. The amino group then detaches from the amino acid, converting it into an α-keto acid; the resulting bound pyridoxamine phosphate on the enzyme then reacts with another α-keto acid, called the amino group acceptor, in a reaction that is the reverse of those described above, to yield a new amino acid and the pyridoxal phosphate–enzyme.

It is this function, which may occur in the absence of the specific enzyme, which suggests that it may be of a prebiotic origin [1,3]. Also, the very ubiquitous reliance of organisms for its function suggests a very early introduction into life processes. This paper outlines an energetically feasible route from molecules presumed to be reasonable constituents of a prebiotic atmosphere on Earth. Although direct evidence is lacking [4,5] it is here assumed to have some of the constituents of the atmosphere of Titan [6–9], namely, cyanoacetylene, diacetylene, and carbon monoxide, and also some of the molecules that have been identified in space, such as ammonia [10] and carbon monoxide [11].



Pyridoxal Phosphate (non zwitterion)

Fig. 1. Pyridoxal phosphate (Vitamin B_6) in an optimum conformation.

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As pyridoxal phosphate is assumed to be a minor constituent from atmospheric reactions, at least one reaction in the sequence of reactions leading to its synthesis is expected to be only marginally favourable, or only kinetically feasible.

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 [12] and GAUSSIAN98 [13] commercial packages, using IBM RISC 6000 and SP2 computers. These computer programs provide a solution to the quantum mechanical Schrodinger equation [14] 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 introduce approximations such as the Born–Oppenheimer Approximation, which allows separation of the electronic and nuclear equations, and 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 [15] 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*.

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. 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 [16].

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 [17], although the cost is higher for the larger molecules.

Since theoretical Hartree–Fock 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. [18].

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 [14].

Most of the atmospheric gaseous reactions considered would be presumed to be able to access considerable activation energy from photochemical excitation [19]. Calculations throughout this paper use the atomic unit of energy [14]: $1\ \mathrm{h} = 4.3597482 \times 10^{-18}$ J [13]. Activation energies are also given in kJ mol^{-1}.

3. Results

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 and 2.

3.2. The formation of initial reactants

The initial reactants are of high intrinsic energy with regard to chemical reactions facilitating exergonic reactions and ultimately the synthesis of the vitamin.

The overall stoichiometry is as follows:

$$\mathrm{H{-}C{\equiv}C{-}CN} + \mathrm{H{-}C{\equiv}C{-}C{\equiv}C{-}H} + \mathrm{CO} + \mathrm{H_2} + \mathrm{H_2O} + \mathrm{H_3PO_4} \longrightarrow \mathrm{C_8H_{10}NO_6P}\ \text{pyridoxal phosphate}$$

$$\Delta H = -0.23372\ \mathrm{h}$$

The initial reactants that need to be justified are the presence of cyanoacetylene and diacetylene. Cyanoacetylene

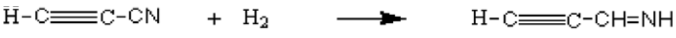
Table 1
HF and MP2/6-31G* total energies and zero point energies (hartrees) for the respective equilibrium geometries

Molecule	HF (hartree)	MP2 (hartree)	ZPE (HF) (hartree)
Diacetylene	−152.49889	−153.00240	0.04203
Cyanoacetylene	−168.54943	−169.07910	0.02989
Prop-2-yne-imine	−169.70389	−170.23556	0.04873
Pent-2,4-diyne-1al	−265.22079	−266.01368	0.05313
4-Ene-4(prop-1-ene-2-yne) imino-2-yne-pent-1-al	−434.98299	−436.30997	0.09936
4-Al-2,5-dimethenyl-3-hydroxyl pyridine	−511.13963	−512.65538	0.14699
4-Al-2,5-dimethenyl-3-hydroxyl pyridine	−511.50563	−513.01308	
4-Al-3-hydroxyl-2-methenyl-5-phosphorylmethyl pyridine	−1153.17228		
Pyridoxal phosphate	−1153.21453	−1155.54543	0.02027
Pyridoxine phosphate	−1154.35953	−1156.72522	

is a major product (as much as 4%) of the action of an electric discharge on a nitrogen–methane mixture [20,21]. The latter may be formed from the photolysis of cyanoacetylene or acetylene [8]. Thus, these two reactants could be considered possible prebiotic molecules for the synthesis. The synthesis proposed involves the formation from the initial reactants of prop-2-yne-imine and pent-2,4-diyne-1al, which subsequently condense to an adduct able to add the elements of water and orthophosphoric acid to give the pyridoxal phosphate. These reactions are described in detail.

3.2.1. The formation of prop-2-yne-imine

In a mildly reducing atmosphere cyanoacetylene might be partially reduced to the imine, amongst other products, as follows:



$$\text{H-C}\equiv\text{C-CN} + \text{H}_2 \longrightarrow \text{H-C}\equiv\text{C-CH=NH}$$

Δ H = 0.00061 h

The reaction is mildly endothermic but should proceed to some extent.

The formal charges on this imine indicate that the nitrogen atom has the largest negative charge and may act as a nucleophilic reagent (Fig. 2).

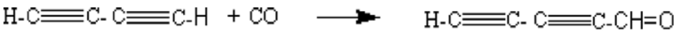
3.2.2. The formation of pent-2,4-diyne-1al

There is a reaction between diacetylene and carbon monoxide, according to the 'oxo' reaction, in which the carbon monoxide adds across the triple bond, followed by a prototropic shift.

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)
H_3PO_4	−642.01033	−642.82036	0.05103
$H_2PO_4^-$	−641.47187	−642.30649	0.04052
CO	−112.73434	−113.02818	0.00484
H_2O	−76.01075	−76.19924	0.02431
H_2	−1.12683	−1.14414	0.01034

This ultimately leads to the formation of the aldehyde [22,23], according to the equation, as shown:



$$\text{H-C}\equiv\text{C-C}\equiv\text{C-H} + \text{CO} \longrightarrow \text{H-C}\equiv\text{C-C}\equiv\text{C-CH=O}$$

Δ H = 0.02247 h

This is a difficult reaction which is slightly endothermic, but both reactants would be able to achieve activation from expected photochemical excitation [24]. However, this is probably the main rate-limiting step. In this bimolecular gas phase reaction, either reactant could become photochemically excited by the absorption of ultraviolet radiation.

The two largest peaks in the UV and vacuum UV spectra of gas phase CO are the peak for the 5σ to 2π* triplet transition at 6.2 eV and the peak for the 5σ to 2π* singlet transition at 8.3 eV. These peaks are clearly evident in the spectra of gas phase CO and are very characteristic of CO [25]. All other peaks in the range 3 to 10 eV are comparatively small.

Similarly, diacetylene in the gas phase absorbs at 4.33 eV attributed to a $^1A_u \leftarrow {}^1\Sigma_g^+$ transition, and at 5.06 eV attributed to a $^1B_u \leftarrow {}^1\Sigma_g^+$ transition [26].

These transitions appear of sufficient energy to overcome the activation energy for the 'oxo' reaction, and also for the further rearrangement to the aldehyde [23].

A calculation of the excited states of the aldehyde using single excitation CI [27], gave the following values (eV) for the excitation energies. Triplet states at: 2.762, 3.503, 3.630, 3.766, 4.468 eV. Singlet states at: 4.046, 4.521, 4.631, 4.948 eV.

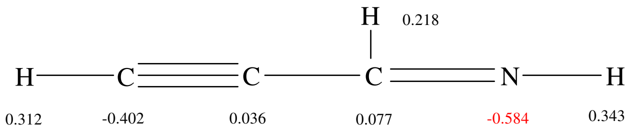


Fig. 2. Calculated formal charges of prop-2-yne-imine (Mulliken) at the MP2 level.

Although the excited state may be involved in dissociation, fluorescence or collisional deactivation, it is the direct reaction,

$$A^* + B \rightarrow C$$

which is described here. The rate of formation of product, C, can be expressed as [24],

$$\frac{\mathrm{d}[C]}{\mathrm{d}t} = \Phi k[A]$$

where the quantum yield, Φ is defined as the ratio of the number of molecules of A^* reacting by that process to the number of photons absorbed, and k, the first order rate constant, is called the specific absorption rate. The first-order rate constant for the formation of an excited species by photolysis is dependent on the absorption cross-section (cm^2) of the molecule A for absorbing radiation of wavelength λ at temperature, T, and the actinic irradiance, F, in units of photons cm^{-2} s^{-1}. The intensity is of the order of 10^{16} photons cm^{-2} s^{-1} at noon [24], and the absorption cross section is often of the order of 10^{-20} cm^2. If the quantum yield is taken as unity (between 0 and 1), then the rate constant is of the order of 10^{-4} s^{-1}. This indicates that reasonable concentrations may be envisaged that would produce an acceptable yield of the aldehyde over a period of time which could be long on an astronomical scale.

The charge distribution in the aldehyde indicates that carbon 4 would be the greatest electrophile, as shown in Fig. 3. The first line of charges, computed by the method of Mulliken [28] are known as Mulliken charges, but as the charge distribution is not observable [29], various other methods of computing the charge are indicated with the designations by which the methods are known in the order Mulliken, Merz–Kollman/Singh [30], CHELP [31], and CHELPG [32].

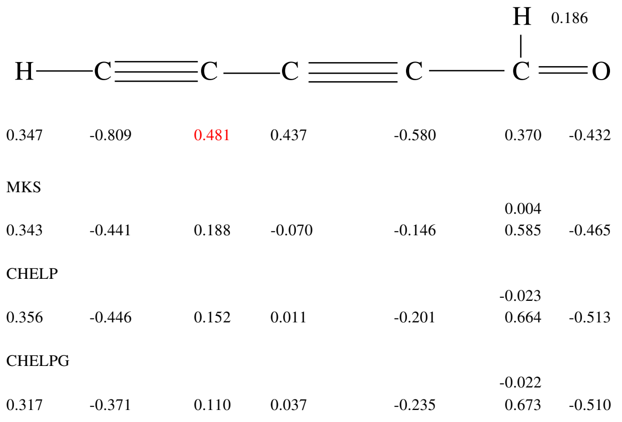


Fig. 3. Calculated formal charges on pent-2,4-diyne-1al calculated in order by the methods of Mulliken [28], MKS [30], CHelp [31], and CHelpG [32], respectively.

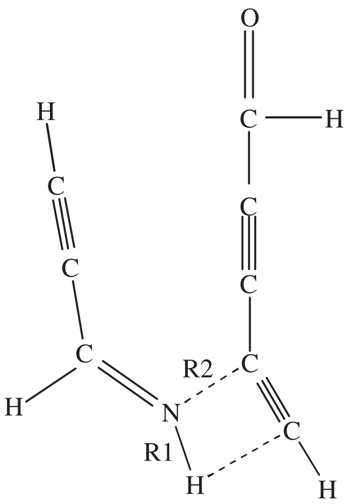
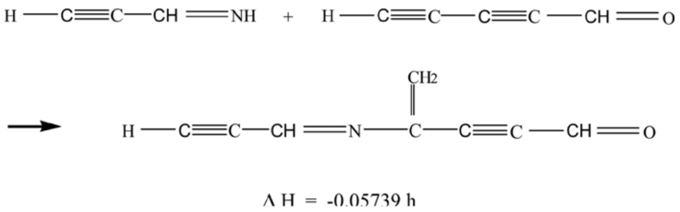


Fig. 4. The transition state for the formation of 4-ene-4(prop-1-ene-2-yne) imino-2-yne-pent-1-al, indicating the internal coordinates used as R1 (N–H) and R2 (N–C).

These methods indicate that nucleophilic attack at the carbon 1 would also be highly competitive. An alternative synthesis involving this route is proposed later.

3.3. The formation of 4-ene-4(prop-1-ene-2-yne) imino-2-yne-pent-1-al

The charge distributions in prop-2-yne-imine and pent-2,4-diyne-1al indicate that nucleophilic attack may occur at carbon 4 to produce the adduct, as shown. This is a general reaction of imines with ynes [33,34].



$$\mathrm{H{-}C{\equiv}C{-}CH{=}NH} + \mathrm{H{-}C{\equiv}C{-}C{\equiv}C{-}CH{=}O} \longrightarrow \mathrm{H{-}C{\equiv}C{-}CH{=}N{-}\overset{\overset{\displaystyle CH_2}{\|}}{C}{-}C{\equiv}C{-}CH{=}O}$$

This is an exothermic reaction, which would be activated by photochemical excitation.

The transition state for the formation of the adduct involves the internal coordinates R1 and R2, as shown in Fig. 4. The potential energy surface is shown in Fig. 5.

The activation energy to form the adduct was calculated as 0.06930 h (182 kJ mol^{-1}), whereas the activation energy to dissociate it was calculated as, 0.12762 h (335 kJ mol^{-1}). It is this adduct which may rearrange and close the ring to form a pyridine.

There would be an expected competing reaction of the imino group with the aldehyde to produce an imino-aldehyde. However, this latter reaction is entirely reversible [35]. The charge distribution in the adduct suggests ring closure may occur initiated by a hydroxyl attack on carbon 2 of the substituted pent-2,4-diyne-1al.

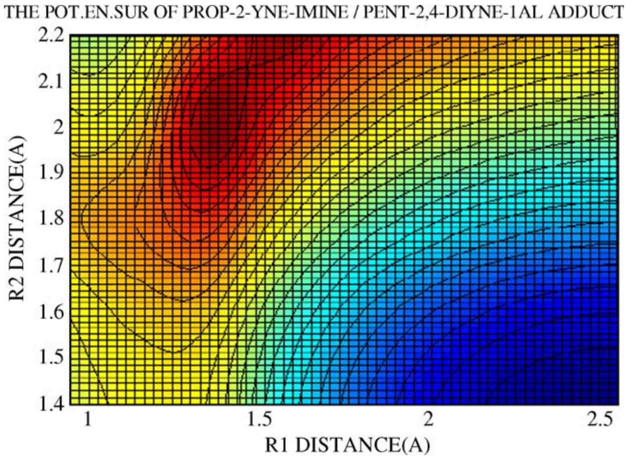


Fig. 5. The potential energy surface for the conversion of prop-2-yne-imine and pent-2,4-diyne-1al to 4-ene-4(prop-1-ene-2-yne) imino-2-yne-pent-1-al. The minimum of the prop-2-yne-imine and pent-2,4-diyne-1al is at (R1 = 0.95, R2 = 2.2). The minimum for the adduct is at (R1 = 2.5, R2 = 1.4). The saddle point is at (R1 = 0.95, R2 = 1.8).

3.3.1. The formation of 4-al-2,5-dimethenyl-3-hydroxyl pyridine

To place the above molecule in the cis conformation shown in Fig. 6, rather than the extended conformation requires only rotation around a single bond, which involves an input of about 6 kcal mol^{-1}. The activation energy to close the ring was calculated by reducing the internal coordinate involving the C–C distance, designated as R in Fig. 7. Without the presence of ions, this was calculated to be 0.06438 h (169 kJ mol^{-1}). The activation energy to open the ring, also without the presence of ions, was calculated as 0.09302 h (244 kJ mol^{-1}). This transition state does suggest that the reaction may well proceed even more easily in the presence of hydrogen and hydroxyl ions, the latter acting as nucleophile, where the charges are conducive to the addition of the elements of water, as shown in Fig. 7.

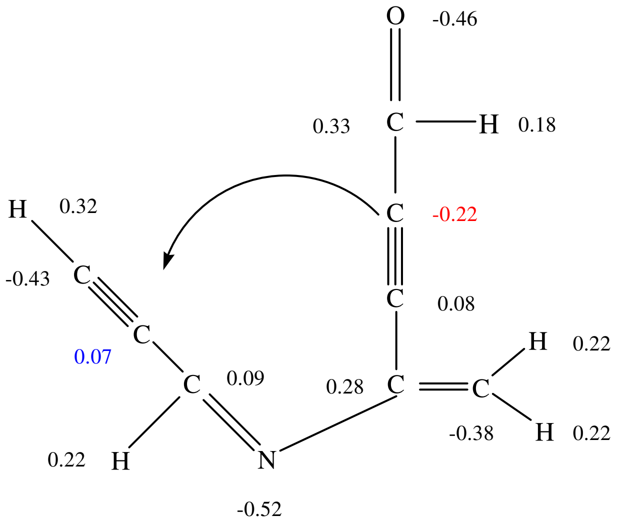


Fig. 6. The *cis* conformation of the adduct of prop-2-yne-imine and pent-2,4-diyne-1al.

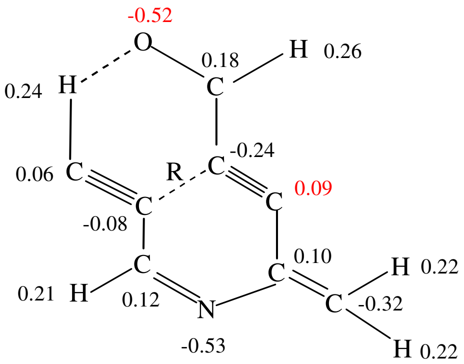
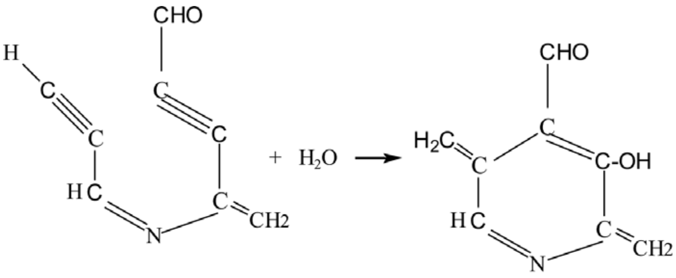


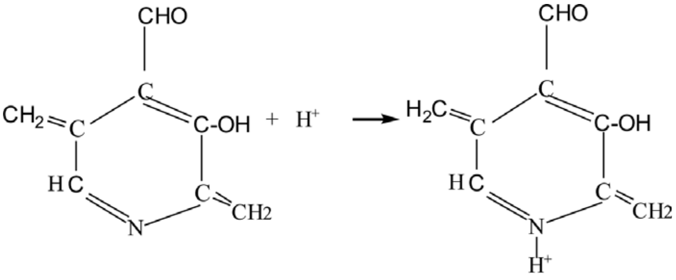
Fig. 7. Formal Mulliken charges in a stable transition state conformation of 4-ene-4(prop-1-ene-2-yne) imino-2-yne-pent-1-al, indicating the internal coordinate, R, for closing the ring.

The ring closure is exothermic and gives the hydroxyl substituent in the correct position, as shown:



$\Delta H = -0.13381$ h

The formal charges on the product indicate that it is most likely to protonate on the nitrogen according to the equation, as shown.



$\Delta H = -0.35770$ h

The reaction is exothermic. The formal charges on the exocyclic methene carbons are about equal, as shown in Fig. 8.

3.3.2. The formation of 4-al-3-hydroxyl-2-methenyl-5-phosphorylmethyl pyridine

Here, the reaction of the 5-methenyl group of the positively charged pyridine is shown interacting with orthophosphate anion. The phosphate anion [36], may be a sufficiently strong

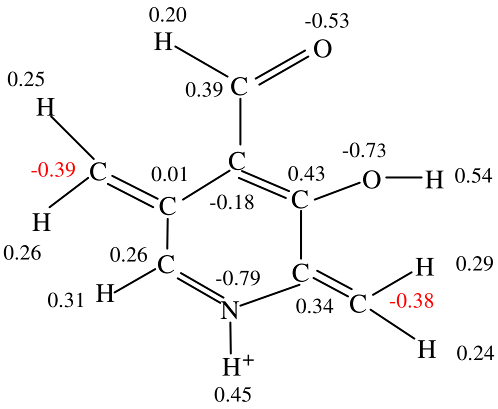


Fig. 8. Formal Mulliken charges on 4-al-2,5-dimethenyl-3-hydroxyl pyridine.

nucleophile to attack this butadiene type of structure to give the zwitterion transition state.

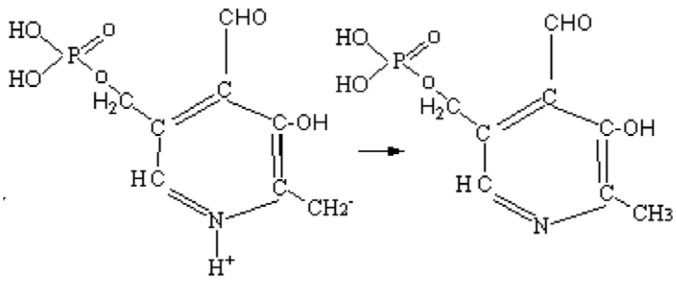
$$\Delta H = -0.19395 \text{ h}$$

The reaction is quite exothermic. There was not any activation energy calculated for the approach of the orthophosphate anion along reaction coordinate O–C bond, R, as shown in Fig. 9, as the reactants were higher in energy than the transition state.

However, the activation energy to dissociate the orthophosphate anion from the ring system was calculated as 0.04567 h (120 kJ mol^{-1}).

3.3.3. The formation of pyridoxal phosphate

This final reaction is a typical acid–base rearrangement to produce a more stable product. The activation energies involving ions are expected to be minimal.



$$\Delta H = -0.04226 \text{ h}$$

The reaction is mildly exothermic.

3.4. An alternative route to pyridoxal phosphate

Whilst the above synthesis is postulated to be the most probable, it is instructive to see if there are other possibilities, and compare the total energy change and the energy changes and activation energies for the respective steps.

3.4.1. Total energies (hartrees)

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

3.4.2. The formation of initial reactants

The initial reactants are of high intrinsic energy with regard to chemical reactions facilitating exergonic reactions and ultimately the synthesis of the vitamin. The overall stoichiometry is as follows:

$$3HC{\equiv}CH + 2\,CO + NH_3 + H_3PO_4 \longrightarrow C_8H_{10}NO_6P + H_2$$

$$\Delta H = -0.22963 \text{ h}$$

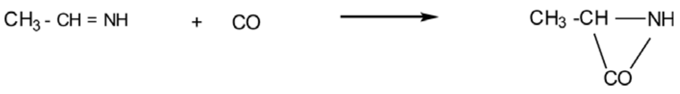
The enthalpy change with these reactants is slightly less than with the previous scheme. The initial reactants that need to be justified are the presence of propargylic aldehyde and 2-methyl-aziridine-3-one.

To justify the presence of these primary substances, the following enthalpy changes have been examined:

3.4.2.1. The formation of 2-methyl-aziridine-3-one. This is conceived as arising from the reaction of carbon monoxide with acetaldimine [35], produced from the reaction of acetylene with ammonia, directly or via acetaldehyde, according to the equation:

$$HC{\equiv}CH + NH_3 \longrightarrow CH_3\text{-}CH{=}NH$$

$$\Delta H = -0.05767 \text{ h}$$



$$\Delta H = 0.03481 \text{ h}$$

The last reaction appears to be the rate-limiting step.

3.4.2.2. The formation of propargylic aldehyde. The reaction of acetylene with carbon monoxide is not energetically favourable, but is feasible, corresponding to a 'oxo' synthesis [22], in which the carbon monoxide adds across the triple bond, followed by a prototropic shift. It is also possible to consider this reaction as arising from a free radical mechanism or facilitated by the H_3^+ ion [11].

$$HC{\equiv}C\text{-}H + CO \longrightarrow HC{\equiv}C\text{-}CO\text{-}H$$

propargylic
aldehyde

$$\Delta H = 0.01414 \text{ h}$$

3.5. The formation of pyridoxal phosphate

As proposed here the pyridoxal phosphate is derived from these 2 moieties that are formed first, namely, 2-methyl aziridine-3-one and propargylic aldehyde.

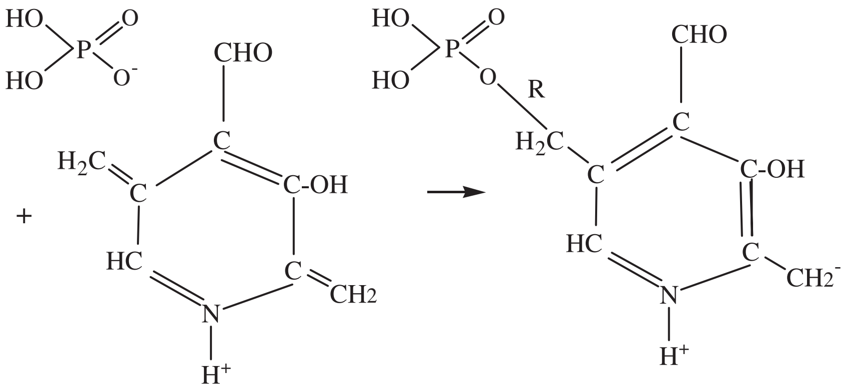
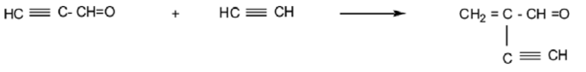


Fig. 9. The formation of 4-al-3-hydroxyl-2-methenyl-5-phosphorylmethyl pyridine along the reaction coordinate R (O–C).

3.5.1. *The formation of 2-methenyl-but-3-yne-1-al*

2-Methenyl-but-3-yne-1-al is considered to be formed from the condensation of propargylic aldehyde and acetylene, as follows, or via the condensation of carbon monoxide with diacetylene. In either case the product is of comparable stability to the linear pent-2-ene-4-yne-1-al.



$$\mathrm{HC{\equiv}C\text{-}CH{=}O} \quad + \quad \mathrm{HC{\equiv}CH} \longrightarrow \mathrm{CH_2{=}\underset{\underset{\displaystyle C{\equiv}CH}{|}}{C}\text{-}CH{=}O}$$

2-methenyl-but-3-yne-1-al

$\Delta H = -0.07024$ h

c.f.

$$\mathrm{HC{\equiv}C\text{-}CH{=}O} \quad + \quad \mathrm{HC{\equiv}CH} \longrightarrow \mathrm{HC{\equiv}C\text{-}CH{=}CH\text{-}CH{=}O}$$

pent-2-ene-4-yne-1-al.

$\Delta H = -0.07208$ h

The overall enthalpy change is favourable.

3.5.2. *The formation of the adduct of 2-methenyl-but-3-yne-1-al and 2-methyl aziridine-3-one*

The prop-2-yne-imine is taken to be a classical nucleophile in attacking the aldehyde group of pent-2-ene-4-yne-1-al, as shown in Fig. 10.

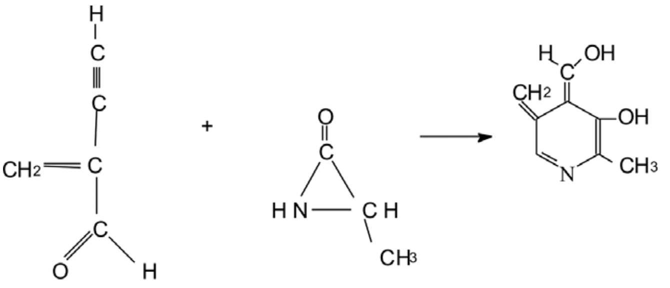
Table 3
HF and MP2/6-31G* total energies and zero point energies (hartrees) for the respective equilibrium geometries

Molecule	HF (hartree)	MP2 (hartree)	ZPE (HF) (hartree)
HC≡CH	−76.81783	−77.06679	0.02945
HC≡C–CH–O	−189.54868	−190.08663	0.04081
HC≡C–C(=CH_2)–CH=O	−266.44384	−267.22961	0.07694
HC≡C–CH=CH–CH=O	−266.43571	−267.23173	0.07726
Acetaldimine		−133.49001	0.07392
2-Methyl-aziridine-3-one	−245.77318	−246.48876	0.08481
3-Hydroxy-5-methenyl-4-methenylol-2-methyl pyridine	−512.29476	−513.81297	0.16974
N-(But-2-methenyl-1-ol-3-ynyl)-2-methyl aziridine-3-one	−512.20433		0.16725

The potential energy diagram for adduct formation indicated an activation energy for adduct formation of 0.0976 h (256 kJ mol^{-1}), whereas the activation energy to dissociate it was calculated as, 0.0860 h (226 kJ mol^{-1}). It is this adduct which may rearrange and close the ring to form a pyridine.

3.5.3. *The formation of 3-hydroxy-5-methenyl-4-methenylol-2-methyl-pyridine*

The imine is taken to be a classical nucleophile in attacking the aldehyde group, followed by ring closure.



3-hydroxy-5-methenyl-4-methenylol-2-methyl-pyridine.

$\Delta H = -0.08748$ h

As the ring closure for this reaction might be considered to have an appreciable activation energy, the potential energy surface was constructed to determine the activation energies to form the five-membered ring and to open the three-membered ring to form the final six-membered ring of pyridoxal phosphate, as shown in Figs. 11 and 12.

The activation energy to close the five-membered ring is 0.07372 h (194 kJ mol^{-1}), whereas the activation energy to open the three-membered ring to finally give the six-membered ring of pyridoxal phosphate is 0.02467 h (65 kJ mol^{-1}). This reaction is expected to be acid–base catalysed so that the actual activation energies could be lower.

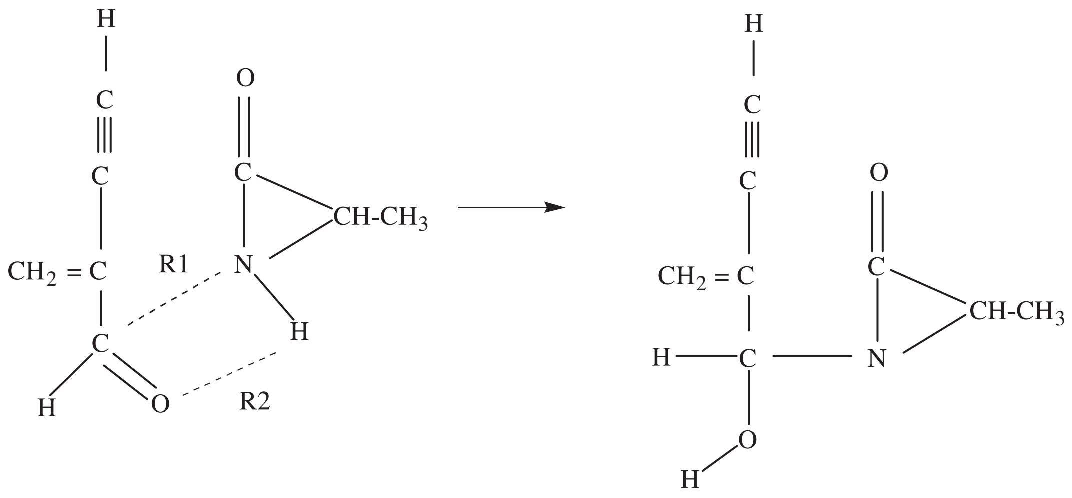
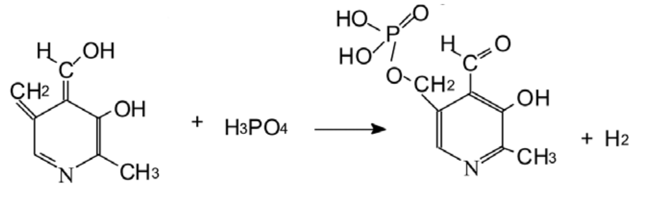


Fig. 10. The transition structure to form the aldehyde ammonia from 2-methyl aziridine-3one and 2-methenyl-but-3-yne-1-al involving the internal coordinates R1 (N–C) and R2 (O–H).

3.5.4. The formation of pyridoxal phosphate

The phosphate anion may be a sufficiently strong nucleophile to attack this butadiene type of structure to give the aldehyde.



3-hydroxy-5-methenyl-4-methenylol-
2-methyl pyridine

pyridoxal phosphate

$$\Delta H_{HF} = -0.03627 \text{ h}$$

4. Discussion

Pyridoxal phosphate is a small stable molecule with comparatively few indications of how it was initially formed to become so essential in transamination. However, with the assumption of readily available reactants in thermodynamically and kinetically viable reactions, at least at low temperatures, in a prebiotic environment, the first synthetic route appears entirely preferred, but not unique. All reactions are at least exothermic except for the rate limiting steps, and the activation energies appear achievable, especially with photochemical excitation.

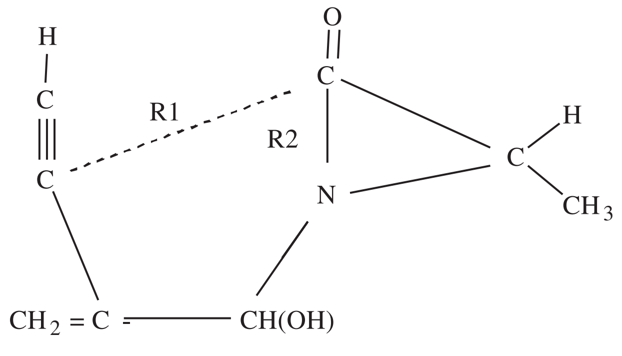


Fig. 11. The transition structure, *N*-(but-2-methenyl-1-ol-3-yne)-2-methyl aziridine-2-one.

From the postulates presented here it is clear that there does appear to be a favourable route to the synthesis of pyridoxal phosphate.

Further work at a higher level of accuracy may result in a correction to the enthalpies calculated here.

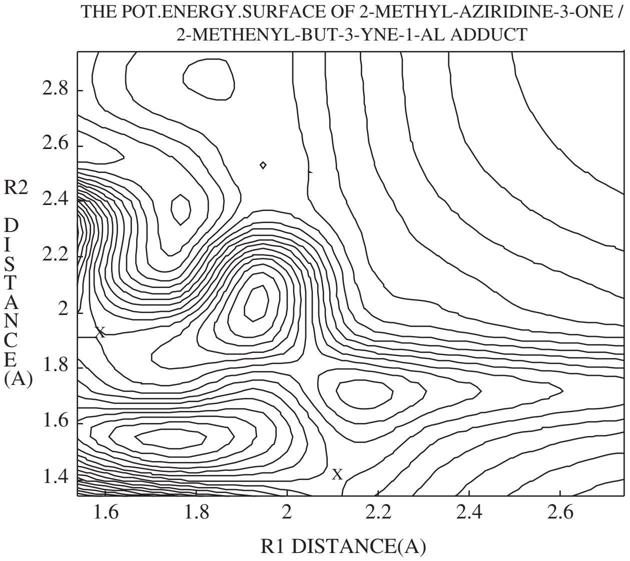


Fig. 12. The potential energy surface for the closure of the five-membered ring resulting from the adduct of 2-methyl-aziridine-3-one and 2-methenyl-but-3-yne-1-al, and the scission of the three-membered ring to give the six-membered ring of pyridoxal phosphate. The adduct possessing the five-membered and three-membered ring has its minimum with internal coordinates, R1 = 1.7 A, R2 = 1.5 A, whereas pyridoxal phosphate has its minimum at internal coordinates, R1 = 1.7 A, R2 = 2.3 A. The influence of ions is neglected for the ring closure in this diagram.

The formation of pyridoxal phosphate is thought to be representative of the prebiotic formation of compounds of major biological significance.

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