A Computational Study of a Prebiotic Synthesis of Folic Acid (Vitamin B9)

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Abstract: - The planetary molecules cyanogen, cyanoacetylene, hydrogen cyanide, ammonia, and carbon monoxide and hydrogen are invoked in a synthesis of the pteridine precursor of the vitamin folic acid. This is followed by the formation of a p-methylamino benzoyl α-glutamic acid from the planetary gases diacetylene, acetylene, hydrogen cyanide, carbon monoxide, ammonia, water and hydrogen. This latter requires a surface catalyzed, photochemically activated synthesis on the magnesium metalloporphyrin catalyst. The addition of several 5-amide glutamic acid entities may be added on the same catalyst surface. Finally the pteridine derivative and the p-methylamino benzoyl-α-glutamic acid derivative are combined to give the folic acid vitamin.
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, and with acceptable activation energies.

Key-Words: - Prebiotic photochemical synthesis, pteridine, p-methylamino benzoyl-α-glutamic acid, Mg.porphin.

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1 Introduction

Folic acid (pteroylglutamic acid), Fig.2, consists of a substituted pteridine, [1], p-aminobenzoic acid, and glutamic acid, [2]. Its derivatives are mainly the tri and hepta γ-glutamyl peptides, [3]. Although folic acid is the vitamin, its reduction products are the actual coenzyme forms, where reduction occurs across the 7,8 bond to give dihydrofolic acid (FH_2), and also across the 5,6 bond to give tetrahydrofolic acid (FH_4) , Fig.1, [3]. The structure has been confirmed by chemical synthesis, [1]. Tetrahydrofolate serves as an intermediate carrier of hydroxymethyl ($-CH_2OH$), formyl (-CHO), or methyl ($-CH_3$) groups in a large number of enzymatic reactions in which the group is transferred from one metabolite to another, or interconverted, involving using the 5 and 10 positions, [1]. The transfer of the one -carbon unit enables the biosynthesis of purines, thymine, serine and glycine [3]. Found in plant leaves such as spinach its deficiency results in failure to grow and forms of anaemia, [2]. The vitamin is produced on an industrial scale and often added as a food supplement, [4], [5]. .
From a prebiotic perspective, [6] it is desirable if the reactant molecules formed spontaneously from a supposed prebiotic atmosphere to be inevitably present. It has often been held that the atmosphere of the Earth was originally mildly reducing, [2], [7], implying the presence of concentrations of carbon monoxide, ammonia, water and hydrogen. It is also supposed that the pteridine was formed from the gases cyanogen, hydrogen cyanide, carbon monoxide, ammonia, acetylene and hydrogen, whilst the p-aminobenzoic acid derivative was formed from diacetylene, acetylene, carbon monoxide and hydrogen. The glutamic acid was formed from acetylene, hydrogen cyanide, carbon monoxide water and hydrogen.
This paper proposes a model for the initial formation of the amino derivative of pteridine which then reacts with a nascent formed benzene derivative.. Final reaction with a glutamic acid or several derivatives [3] yielding the folic acid vitamin(s). The p-aminobenzoic acid formation is described as requiring the Mg.porphin catalyst.
These reactions are assumed to occur mainly in the liquid phase [8].
The reactions described have been deduced as kinetically and thermodynamically viable, but photochemical excitation is required.

2 Problem Formulation

This proposed computational study of a plausible synthesis of the vitamin folic acid involves the calculation of the enthalpy changes for reaction intermediates in the ZKE approximation and the calculation of activation energies at the HF level. These activation energies may all be accessible as the catalyst may absorb appreciable photochemical activation (0.21 h). The computations tabulated in this paper used the GAUSSIAN09, [9].

The standard calculations at the HF and MP2 levels including zero-point energy corrections at the Hartree Fock level, [10], together with scaling, [11], using the same basis set, 6-31G*, are as previously published, [6]. Enthalpy changes at the MP2 level not including scaled zero point energies are designated as $\Delta H_{(MP2)}$. The charge transfer complexes are less stable when calculated at the Hartree Fock level, [10], and activation energies calculated at the HF level without scaling are less accurate.

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. This paper uses the atomic unit of energy, the hartree, [9].

1h = 627.5095 kcal.mol^{-1}. 1h = 4.3597482 x 10^{-18} J

Mullikan charges are in units of the electronic charge.

3 Problem Solution

3.1 Total Energies (hartrees)

The initial reactants in this proposed prebiotic synthesis of folic acid are simple gases, cyanogen, hydrogen cyanide, carbon monoxide, ammonia and hydrogen.

However, the immutable laws of chemical thermodynamics and kinetics dictate unequivocally that a cascade of further reactions is inevitable irrespective of the concentrations of reactants provided the physical conditions are conducive to chemical reactions.

Some of the reactions that may be expected in the gaseous and liquid phase are given here as forming the initial reactant molecules to synthesize folic acid.

The gas cyanogen [12] may be formed by the reaction assumed to be mediated by free radicals as,

$$2\ \underset{(1)}{H\text{-}C\equiv N} \rightarrow \underset{(2)}{N\equiv C - C\equiv N} + H_2$$

$\Delta H =$ -0.00603 h

Also, the formation of cyano acetylene [8] as,

$$\underset{(2)}{H\text{-}C\equiv N} + \underset{(3)}{H\text{-}C\equiv C\text{-}H} \rightarrow \underset{(4)}{N\equiv C - C\equiv C\text{-}H}$$

$\Delta H =$ -0.00187 h

The formation of diacetylene as,

$$2\ H\text{-}C\equiv C\text{-}H \rightarrow \underset{(5)}{H\text{-}C\equiv C - C\equiv C\text{-}H} + H_2$$

$\Delta H =$ -0.01855 h

The formation of cyanamide as,

$$H\text{-}C\equiv N + NH_3 \rightarrow \underset{(6)}{NH_2\text{-}C\equiv N} + H_2$$

$\Delta H =$ 0.01808 h

Followed by the formation of guanidine, as,

$$NH_2\text{-}C\equiv N + NH_3 \rightarrow \underset{(7)}{(NH_2)_2\text{-}C{=}NH}$$

$\Delta H =$ -0.01357 h

These further reactants are expected to have been present at some concentration over eons predicated on the Earth's atmosphere being mildly reducing at some time past.

The intermediates by which these could form folic acid are listed in Table 1. The catalyst for the formation of the p-amino benzoyl grouping is Mg.porphin.

The standard numbering nomenclature for pterin derivatives is given in Fig.1, [13]

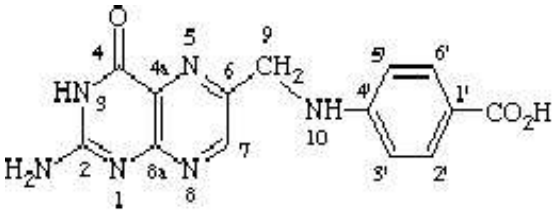


Fig.1 The standard numbering for pterioic acid

These complexes are integral reactants in the proposed synthesis. The energies of the stable complexes to form the pteridine and amino benzoyl derivative are shown in Table 1.

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

Molecule	HF hartree	MP2 hartree	ZPE (HF) hartree
hydrogen cyanide (1)	-93.15894		0.01593
cyanogen (2)	-185.17464		0.01550
ethyne (3)	-77.06680		0.02945
cyanoacetylene (4)	-169.07910		0.02989
diacetylene (5)	-153.00240		0.04203
cyanamide (6)	-148.35090		0.03702
guanidine (7)	-204.73053		0.08206
folic acid (8)	-1565.55985		0.42011
2-amino 6-aminomethanyl 4-hydroxy pteridine (9)	-673.32666		0.17972
1-methylamino carbonyl 4-methylamino benzene (10)	-533.21885		0.21528
2-cyano azirinone (11)	-298.11914		0.02762
2-guanidino 2-keto 2-dehydroimido ethyl cyanide (12)	-502.93311		0.11586
2-amino 1:2-dihydro 4-keto 5-imido-6-imido 1:3 -diazine (13)	-502.86045		0.11547
2-imino 4-hydroxy 5,6-di-imido 1,3-diazine (14)	-502.93408		0.11769
2-amino 6-cyano 5,8 dihydro 4-hydroxy pteridine (15)	-672.13101		0.15568
2-amino 6-cyano 4-hydroxy pteridine (16)	-668.98002	-670.98089	0.12904
2-amino 6-cyano 7,8-dihydro 4-hydroxy pteridine (HF) (17)	-670.14430		0.14445
2-amino 6-cyano 4-hydroxy 5,6,7,8-tetrahydro pteridine (HF) (18)	-671.30983		0.16194
2-amino 4-hyfroxy 5,8 dihydro 6-aminomethanyl pteridine (19)	-673.32666		0.17972
Mg.1, but-1,3-diyn-1yl.porphin.ethynyl (20)	-1415.18777		0.35948
Mg.1,2,3-didehydro phenyl.porphin (21)	-1415.31316		0.36700
Mg.1, phenyl.porphin (22)	-1416.6070		0.39442
Mg.1,4-methyl ammonium phenyl.porphin (23)	-1510.82903		0.44332
Mg.1 porphin.4-methyl ammonium phenyl (24)	-1570.75146		0.44090
Mg.1, CO.porphin.4-methyl ammonium phenyl (25)	-1623.79160		0.45860
Mg.1, 4-methyl ammonium carbon-1-yl.porphin (26)	-1623.85187		0.45327
Mg.1,porphin. 4-methyl ammonium phenyl carbon-1-yl (27)	-1623.89273		0.46363
Mg.1,1-methyl ammonium carbon-1-yl 4-methyl ammonium phenyl.porphin (28)	-1719.48434		0.53885
1-methyl amino carbonyl 4-methyl amino benzene (29)	-533.21885		0.21528
Mg.porphin (1) (14)	-1185.12250		0.29262
CO	-113.02122		0.00566
$OH^{\cdot}$	-75.52257		0.00911
OH^{-}	-75.51314		0.00816
H_2O	-76.19685		0.02045
NH_3	-56.35421		0.03700
H_2	-1.14414		0.01056

3.2 The overall stoichiometry for the formation of the folic acid.

The overall stoichiometry to form the folic acid is as follows,

$$N \equiv C - C \equiv N + (NH_2)_2\text{-}C{=}NH + NC\text{-}C \equiv C\text{-}H + 4\ CO + 2H\text{-}C{\equiv}C\text{-}H + HCN + 2H_2O + H\text{-}(C{\equiv}C)_2\text{-}H + H_2 \rightarrow C_{19}N_7O_6H_{19}$$

folic acid

$$\Delta H = -0.57160 \text{ h}$$

To save computer time the molecule is approximated by three simpler molecules, as

2-amino 6-aminomethanyl 4-hydroxy pteridine (The pteridinyl precursor) formed from,

$N \equiv C - C \equiv N + (NH_2)_2\text{-}C{=}NH + NC\text{-}C \equiv C\text{-}H + CO + H_2 \rightarrow C_7N_6OH_8$

$\Delta H = -0.14485$ h

The 1-methylamino carbonyl 4-methylamino benzene (The p-methylamino benzoyl methylamide) formed as,

$H\text{-}(C \equiv C)_2 - H + H\text{-}C \equiv C\text{-}H + CO + 2CH_3NH_2 \rightarrow C_7N_2OH_6$

$\Delta H = -0.24885$ h

The glutamic acid (The amide residue) formed as,

$H\text{-}C{\equiv}C\text{-}H + 2H\text{-}CN + 2CO + 2H_2O + H_2 \rightarrow C_5N\,O_4H_9$ glutamic acid

$\Delta H = -0.19326$ h

It is assumed that the enthalpy chages involved in the synthesis of these three simpler molecules are the same as those involved in the formation of the folic acid molecule, as,

2-amino 6-aminomethanyl 4-hydroxy pteridine + 1-methylamino carbonyl 4-methylamino benzene + glutamic acid → pteroyl glutamic acid + $2CH_3NH_2$

$\Delta H = -0.58696$ h

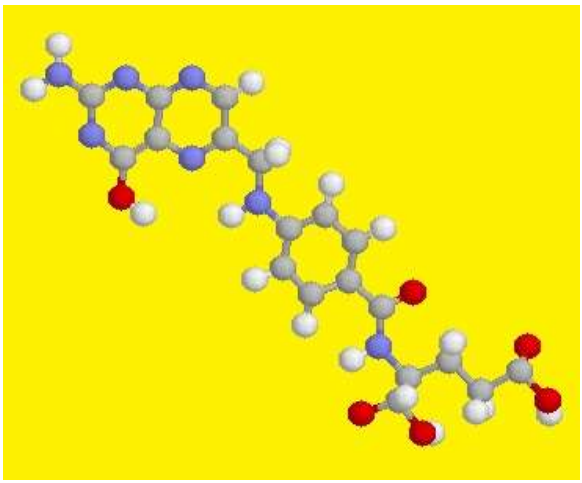


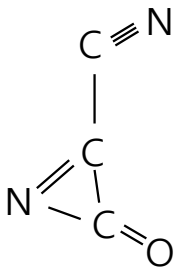
Fig.2. folic acid (8)

The enthalpy change is negative indicating that this may be the energetically favourable route to the initial formation of the folic acid. The intermediates by which these stoichiometric reactions may have occurred are as follows:
Molecules are numbered consecutively.
Subsections depict alternatives in the sequence of the reaction mechanism.
A standard numbering of the atoms in pteridine is as shown in Fig.1, [3], [12].

3.3 The formation of 2-cyano azirinone

Carbon monoxide is known to react with cyanides and imines to form high energy strained azirinones and aziridones. The reaction with cyanogen is depicted here as a gas phase condensation reaction,

$CO + N \equiv C - C \equiv N \rightarrow$
(1) (2)



2-cyano azirinone (11)

$\Delta H = 0.07283$ h

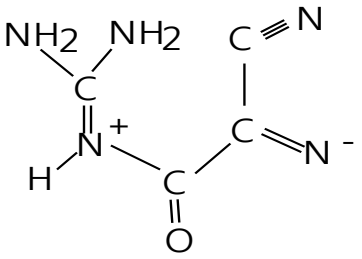
The reaction appears marginally feasible.

The activation energy for the forward reaction was calculated as 0.070 h and 0.01 h for the reverse reaction.

3.4 The formation of 1-dehydroimido 2-guanidino 2-keto ethyl cyanide

A guanidine molecule may be expected to react with the high energy 2-cyano azirinone as,

$(NH_2)_2$-C=NH + N==C-CN →
\CO/
(1) (3)



1-dehydroimido 2-guanidino 2-keto ethyl cyanide. (12)

$$\Delta H = -0.07794 \text{ h}$$

The potential energy diagram for the formation of 1-dehydroimido 2-guanidino 2-keto ethyl cyanide is given in Fig.

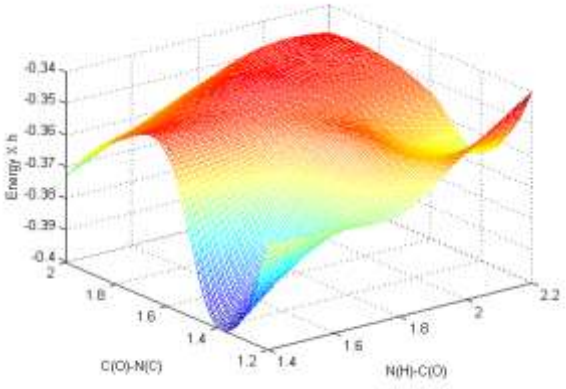


Fig.2. The potential energy diagram for the formation of 1-dehydroimido 2-guanidino 2-keto ethyl cyanide where the x-axis is the N(H) –C(O) and the y-axis the N(C)-C(O) bond extension. The reactants are at at (2.5,1.4), the 1-dehydroimido 2-guanidino 2-keto ethyl cyanide at (1.4,1.4), the saddle point at (2.0,1.4). The energy = -501.0 + X h.

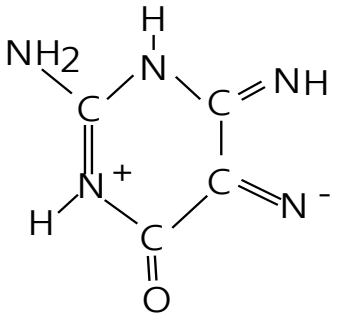
At HF level the activation energy for the addition was 0.014 h and 0.027 for the reverse reaction.
The combined energy for the addition of the two adducts carbon monoxide and guanidine to cyanogen is then,

$$\Delta H = -0.00511 \text{ h}$$

3.5 The formation of 2-amino 5-dehydroimido 6-imido 4-keto 1:2-dihydro 1:3 -diazine

Further condensation may result in ring closure in a nucleophilic addition reaction as,

1-dehydroimido 2-guanidino 2-keto ethyl cyanide →



2-amino 5-dehydroimido 6-imido 4-keto 1:2-dihydro 1:3 -diazine (13)

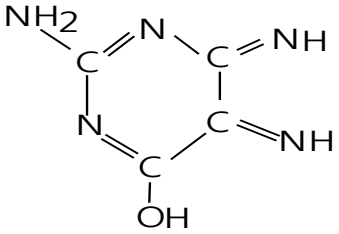
$$\Delta H = 0.07232 \text{ h}$$

The addition reaction is favourable and treated as a transfer reaction involving ring closure. The activation energy for the ring closure was the same as the enthalpy change with the reverse reaction activation energy being 0.010 h.

3.6 The formation of 2-amino 5,6-di-imido 4-hydroxy 1,3-diazine

A prototropic shift results in a favourable enthalpy change as,

2-amino 5-dehydroimido 6-imido 4-keto 1:2-dihydro 1:3 -diazine → [8]



2-amino 5,6-di-imido 4-hydroxy 1,3-diazine (14)

$$\Delta H = - 0.07165 \text{ h}$$

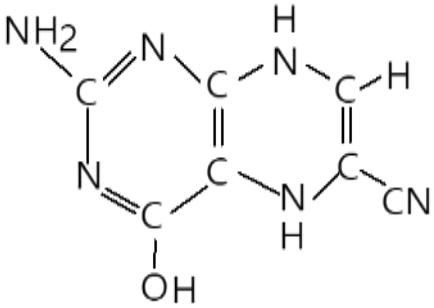
The hydrogen shift involves a negligible activation energy.
The combined energy change for these two reactions is then,

$$\Delta H = - 0.00562 \text{ h}$$

3.7 The formation of 2-amino 6-cyano 5,8 dihydro 4-hydroxy pteridine

The 2-amino 5,6-di-imido 4-hydroxy 1,3-diazine is susceptible to 1:4 addition reactions. One is represented here as reaction with cyanoacetylene to give a pteridine depicted here as,

2-amino 4-hydroxy 5,6-di-imido 1,3-diazine + cyanoacetylene → [9]



2-amino 6-cyano 5,8 dihydro 4-hydroxy pteridine (15)

ΔH = -0.11062 h
The potential energy diagram is given in Fig.

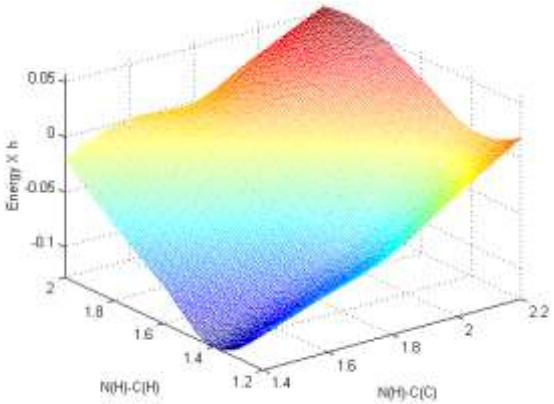


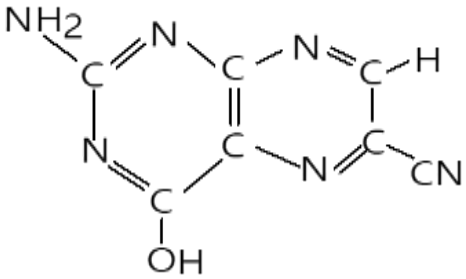
Fig.2. The potential energy diagram for the formation of 2-amino 6-cyano 5,8 dihydro 4-hydroxy pteridine where the x-axis is the N(H) –C(CN) and the y-axis the N(H)-C(H) bond extension. The reactants are at at (2.5,1.4), the 2-amino 6-cyano 5,8 dihydro 4-hydroxy pteridine at (1.4,1.4), the saddle point at (2.0,1.4). The energy = -670.0 + X h.

No activation energy could be determined for this 1:4 condensation reaction.

3.8 The formation of 2-amino 6-cyano 4-hydroxy pteridine

The 2-amino 6-cyano 5,8 dihydro 4-hydroxy pteridine may lose hydrogen as.

2-amino 6-cyano 5,8 dihydro 4-hydroxy pteridine → H_2 +



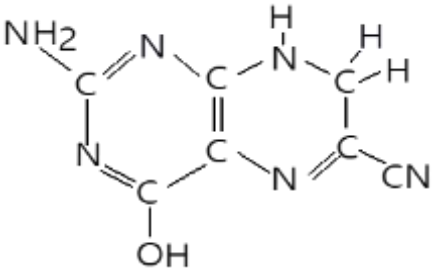
2-amino 6-cyano 4-hydroxy pteridine. (16)

ΔH = -0.00831 h
The activation energy was the same as the enthalpy change.
The enthalpy change gives the order of the reduction reaction.

3.8.1 The formation of 2-amino 6-cyano 7,8-dihydro 4-hydroxy pteridine

The 2-amino 6-cyano 4-hydroxy pteridine may add a molecule of hydrogen across the 7-8 bond as,

2-amino 6-cyano 4-hydroxy pteridine + H_2 →



2-amino 6-cyano 7,8-dihydro 4-hydroxy pteridine (17)

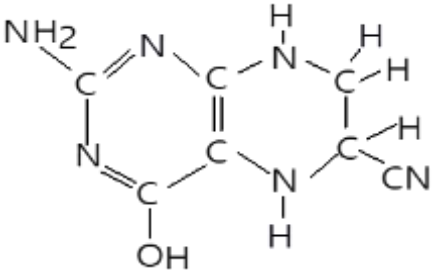
$$\Delta H_{(HF)} = -0.023128 \text{ h}$$

This is of the same order as the first dehydrogenation.

3.8.2 The formation of 2-amino 6-cyano 4-hydroxy 5,6,7,8-tetrahydro pteridine

The 2-amino 6-cyano 7,8 dihydro 4-hydroxy pteridine may add a molecule of hydrogen across the 5-6 bond as,

2-amino 6-cyano 7,8-dihydro 4-hydroxy pteridine + H_2 →



2-amino 6-cyano 4-hydroxy 5,6,7,8-tetrahydro pteridine (18)

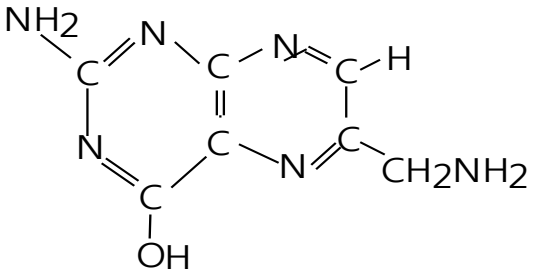
$$\Delta H_{(HF)} = -0.02434 \text{ h}$$

This is of the same order as the first dehydrogenation.

3.9 The formation 2-amino 4-hydroxy 6-aminomethanyl pteridine

The 2-amino 6-cyano 4-hydroxy pteridine may be reduced by hydrogen radicals or hydrogen molecules as, [15], as,

2-amino 6-cyano 4-hydroxy pteridine + H_2→ [10]



2-amino 4-hydroxy 6-aminomethanyl pteridine (19)

$$\Delta H = -0.03122 \text{ h}$$

.

The hydrogenation is favourable, requiring negligible activation energy with hydrogen radicals or molecular hydrogen.

The combined enthalpy changes to form 2-amino 4-hydroxy 6-aminomethanyl pteridine is then calculated as,

$$\Delta H = -0.14485 \text{ h}$$

With the completion of the synthesis of the 2-amino 4-hydroxy 6-aminomethanyl pteridine entity, this may be substituted by methylamine to save computer time.

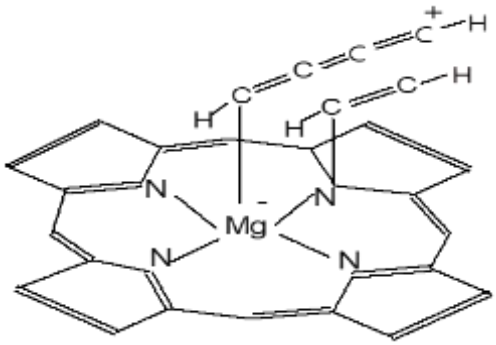
The second substituent to be formed is methyl ammonium carbonyl 4-methylammonium phenyl on the Mg.porophin catalyst.

3.10 The formation of Mg.1, but-1,3-diyn-1y.porphin.ethynyl

This is here depicted as requiring a catalyst,

First, the benzoyl entity needs to be formed, as arising from the addition of diacetylene and acetylene to the Mg.porphin catalyst, as,

H-C≡C-C≡C-H + H-C≡C-H + Mg.porphin →



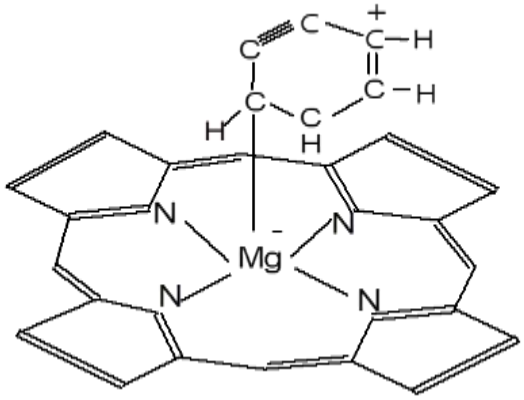
Mg.1, but-1,3-diyn-1yl.porphin.ethynyl
(20)
ΔH = -0.00018 h

These charge transfer complexes form spontaneously, [16]

3.11 The formation of Mg.1,2,3-didehydro phenyl.porphin

Ring closure of the di-adduct is feasible as,

Mg.1, but-1,3-diyn-1yl.porphin.ethynyl
→



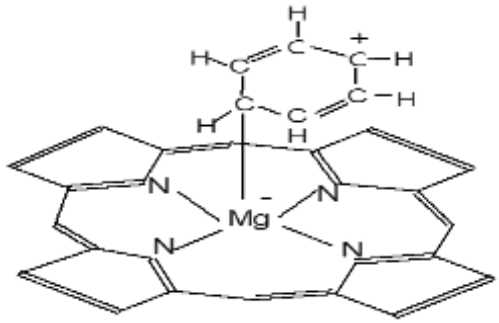
Mg.1,2,3-didehydro phenyl.porphin
(21)

ΔH = -0.11870 h
The activation energy was calculated as 0.0 h, as they spontaneiously coalesce.[17]

3.12 The formation of Mg.1, benzyn-1yl.porphin

The Mg.1,2,3-didehydro phenyl.porphin may be hydrogenated in a feasible reaction, as,

Mg.1,2,3-didehydro phenyl.porphin
+ H_2 →



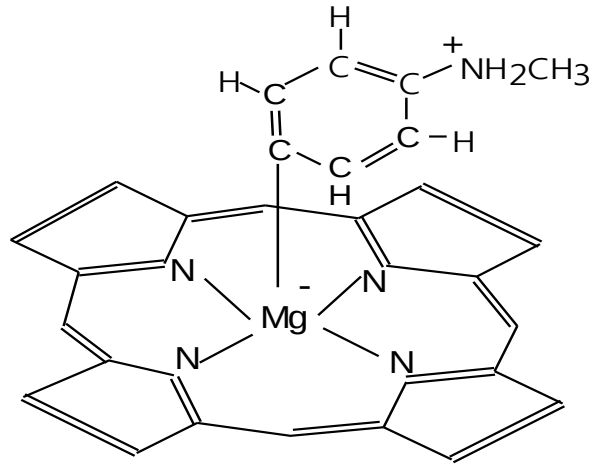
Mg.1, phenyl.porphin
(22)

ΔH = - 0.13472 h
The activation energy for the hydrogenation was negligible with hydrogen radicals or molecular hydrogen.
.

3.13 The formation of Mg.1, 4-methyl ammonium phenyl.porphin

The Mg.1, phenyl.porphin may react with an amine to form a substituted ammonium compound. To conserve computer time, this is represented here as methylamine addition ,as,

Mg.1, phenyl.porphin + CH_3NH_2 → H_2 +
(11)

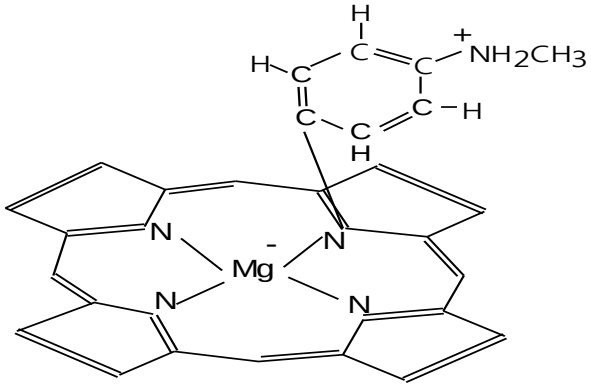


Mg.1,4-methyl ammonium phenyl.porphin
(23)
ΔH = 0.13240 h
The activation energy and enthalpy change for this reaction are assumed to arise from the first excitation of the Mg.porphin catalyst, 0.21 h..

3.14 The formation of Mg.1, porphin.4-methyl ammonium phenyl

The Mg.1,4-methyl ammonium phenyl. porphin may be promoted to a higher energy state as,

Mg.1,4-methyl ammonium phenyl.porphin → [15]



Mg.1 porphin.4-methyl ammonium phenyl (24)

ΔH = -0.03154 h

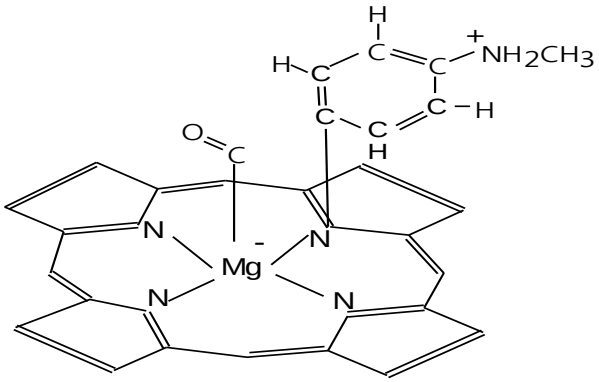
.

The activation energy was the same as the enthalpy change.

3.15 The formation of Mg.1, CO.porphin.4-methyl ammonium phenyl

The Mg.1,.porphin.4-methyl ammonium phenyl may accommodate a carbon monoxide adduct on the free Mg.porphin site as,

Mg.1,porphin.4-methyl ammonium phenyl + CO →



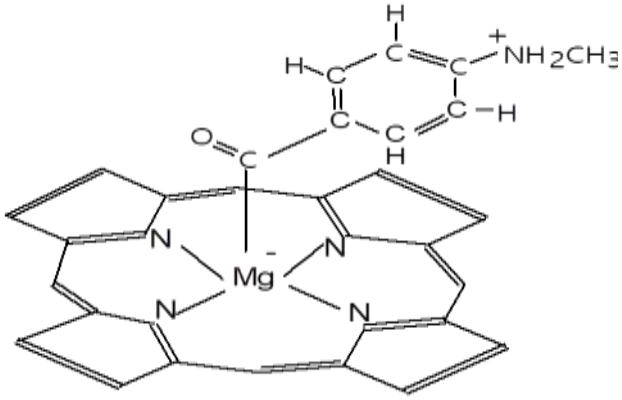
Mg.1, CO.porphin.4-methyl ammonium phenyl (25)

ΔH = -0.00812 h

3.16 The formation of Mg.1, 4-methyl ammonium phenyl carbon-1-yl .porphin

The Mg.1, CO.porphin.4-methyl ammonium phenyll adducts may coalesce as,

Mg.1, CO.porphin.4-methyl ammonium phenyl →



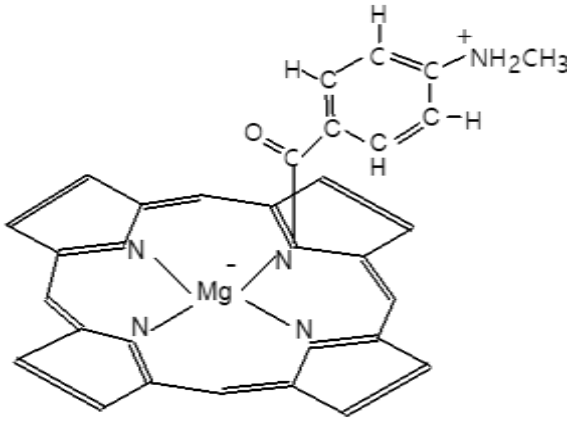
Mg.1, 4-methyl ammonium carbon-1-yl.porphin (26)

ΔH = -0.06512 h

3.17 The formation of Mg.1,porphin. 4-methyl ammonium phenyl carbon-1-yl

The Mg.1, 4-methyl ammonium carbon-1-yl.porphin may be excited to a higher energy state as,

Mg.1, 4-methyl ammonium carbon-1-yl.porphin →



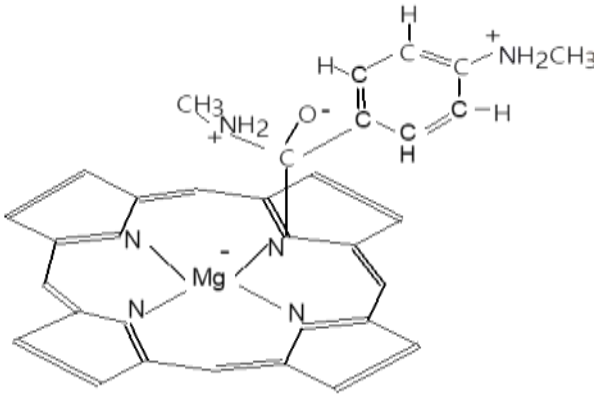
Mg.1,porphin. 4-methyl ammonium phenyl carbon-1-yl (27)

ΔH = -0.03154 h

3.18 The formation of the Mg.1, porphin.1-methyl ammonium carbon-1yl 4-methyl ammonium phenyl

The Mg.1, 4-methyl ammonium carbon-1-yl.porphin may react with methylamine to form a viable, stable complex as,

Mg.1, porphin 4-methyl ammonium carbon-1-yl.porphin + CH_3NH_2 →



Mg.1,porphin 1-methyl ammonium carbon-1-yl 4-methyl ammonium phenyl
(28)

$$\Delta H = -0.07890 \text{ h}$$

3.19 The formation of 1-methyl ammonium carbonyl 4-methyl ammonium benzene

The Mg.1,1-methyl ammonium carbon-1-yl 4-methyl ammonium phenyl.porphin adduct is rendered unstable in the presence of hydrogen [15] or hydroxyl radicals or hydroxide anions and discharges. The adduct may then separate from the catalyst as,

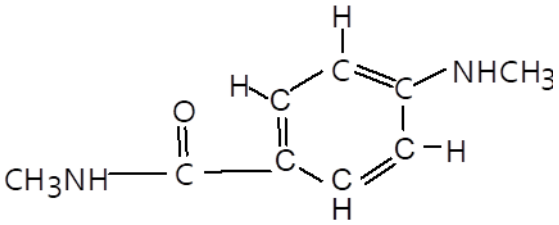
$H_2 \rightarrow 2\,H\cdot$

$\Delta H = 0.13825$ h

Mg.1,porphin.1-methyl ammonium carbon-1-

yl 4-methyl ammonium phenyl + $2H^{\bullet}$ →

Mg.porphin + $2H_2$ +



1-methyl amino carbonyl 4-methyl amino benzene (29)
(15)

$\Delta H = -0.15766$ h

3.20 The formation of pteroylglutamic acid

For the explicit formation of folic acid it is assumed that the enthalpy changes recorded for the above, 1-methyl amino carbonyl 4-methyl amino benzene, are the same as those for the formation of folic acid. Here the first methylamino group is replaced by the pteridino residue and the the second methylamino residue by the glutamic acid, according to the equation,

2-amino 4-hydroxy 6-aminomethanyl pteridine + 1-methyl amino carbonyl 4-methyl amino benzene + glutamic acid →

pteroylglutamic acid + 2 methylamine.

$\Delta H = -0.58696$ h

Fig.2.. pteroylglutamic acid

4. Conclusion

The formation of L-glutamic acid has been depicted as requiring photochemical excitation on a surface catalyst such as the Mg.porphin used here, [17]. Whilst it could react with the Mg.1,porphin. 4-methyl ammonium phenyl carbon-1-yl as depicted above using methylamine as substituent it could also react in the form of its prebiotic precursor 2-cyanoethyl aziridine-3-one which is strained and highly reactive. It is formed on the same catalyst molecule and may coordinate with the coordination site rendering any entropy change as minimal. A mechanism for successive addition of glutamic acid residues . on the catalyst surface has been suggested as a

general method of peptide or protein synthesis, [ ]. However the glutamic acid residues added are recorded as often being formed by bonding with the γ-carboxyl grouping, suggesting that the appropriate aziridone from pyroglutamic was available. The adducts on this catalyst surface may in general occupy both high and low energy sites allowing each to be a reactive nucleophile.

The reactions do appear to be thermodynamically viable with acceptable activation energies and inevitable. The existence of this molecule in hydrogen transport reactions and its widespread occurrence in biochemistry does suggest it is of extreme antiquity.

Further work at a higher accuracy may alter the values given here.

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