A Computational Study of a Prebiotic Synthesis of D-Riboflavin (Vitamin B2)

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Abstract: - Ab initio applied computing is used to determine the viability of a plausible mechanism for the formation of riboflavin from planetary and interstellar gases that contain the necessary essential elements. The immutable laws of chemical thermodynamics and kinetics enable the intermediates in the synthesis to be characterized and the activation energies to be established. The gases propyne, cyanogen, carbon monoxide, and hydrogen are invoked in a synthesis of the isoalloxazine precursor of the vitamin riboflavin (Vitamin B_2), whilst the additional presence of hydrogen cyanide enables the surface-catalyzed, photochemically activated synthesis of a D-ribitylamine requiring the magnesium metalloporphyrin catalyst. These two molecules then bond in a Sn2 reaction to form the final vitamin structure.
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, isoalloxazine, D-ribitylamine, riboflavin, (vitamin B_2), Mg.porphin

Received: July 29, 2022. Revised: October 4, 2023. Accepted: October 17, 2023. Published: November 1, 2023.

1 Introduction

Riboflavin (Vitamin B_2) consists of the sugar D-ribitol bonded to a substituted isoalloxazine ring, Figure 1 and Figure 6. The vitamin occurs as a constituent of the two flavin coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) where the sugar is D-ribitol rather than D-ribose, [1]. The structure has been confirmed by chemical synthesis, [2], [3]. These enzymes belong to the group of flavoproteins which catalyze oxidation-reduction reactions where the prosthetic coenzymes FMN and FAD are firmly associated with the protein component, [1]. Reversible reduction of the isoalloxazine ring yields $FMNH_2$ and $FADH_2$ in the mononucleotide and dinucleotide, respectively, where the reduction of the flavin coenzyme may involve a semiquinone, [1]. The metalloflavoproteins contain one or more metals as additional cofactors, [4]. Riboflavin (vitamin B2), is a water-soluble vitamin, an essential nutrient in higher organisms as it is not endogenously synthesized, [5]. It is essential for redox reactions necessary for energy production, antioxidant protection, and metabolism of other B vitamins, such as niacin, pyridoxine, and folate, [6]. Flavins have been recognized as being capable of both one- and two-electron transfer processes, and as playing a pivotal role in coupling the two-electron oxidation of most organic substrates to the one-electron transfers of the respiratory chain, [7], [8]. Research is attempting to incorporate gases into the synthesis of riboflavin, [9].

From a prebiotic perspective, [10], 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, [4], [11], implying the presence of concentrations of carbon monoxide, ammonia, water, and hydrogen. It is also supposed that the isoalloxazine was formed from the gases propyne, cyanogen, carbon monoxide, and hydrogen, whilst the D-ribitol entity was formed from carbon monoxide, hydrogen cyanide, and hydrogen.

This paper proposes a model for the initial formation of the isoalloxazine present as an anion. The D-ribose is described as being formed on a Mg.porphin catalyst from the most abundant gases carbon monoxide and hydrogen. which determines the stereochemistry. It is present as a ribityl ammonium compound.

These two molecules then combine in a Sn2 substitution reaction.to form the riboflavin vitamin.

These reactions are assumed to occur mainly in the liquid phase, [12].

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 riboflavin 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, [13].

The standard calculations at the HF and MP2 levels including zero-point energy corrections at the Hartree Fock level, [14], together with scaling, [15], using the same basis set, 6-31G*, are as previously published, [10]. Gibbs free energy calculations at 298.15 K and 1 atmosphere use the HF model, basis set 6-31G*, and the zero point energy is not scaled. The charge transfer complexes are less stable when calculated at the Hartree Fock level, [14], 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, [13].
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 riboflavin are simple gases, propyne, cyanogen, hydrogen cyanide, carbon monoxide, and hydrogen. The intermediates by which these could form riboflavin are listed in Table 1. The catalyst for the formation of D-ribose is Mg.porphin.

These complexes are integral reactants in the proposed synthesis. The energies of the stable complexes to form the isoalloxazine and D-ribitylamine are shown in Table 1.

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

Molecule	MP2 hartree	ZPE (HF) hartree
propyne (1)	-116.24181	0.06010
cyanogen (2)	-185.17464	0.01550
4-imido but-2-yn cyanide (3)	-301.40714	0.08417
4,5-di-imido octan-2,6-diyne (4)	-417.67097	0.14999
4- (2-cyano 1-methanimido)-imido-5-imido octan-2,6-diyne (5)	-602.86341	0.17215
2,3-di-imido 5.6-dipropynyl 1,4-pyrazine (6)	-602.85931	0.17456
2,3-di-aziridon-2yl 5.6-dipropynyl 1,4-pyrazine (7)	-828.84266	0.19630
2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine (8)	-829.03869	0.19824
1-dehydro 2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine^{-} (9)	-828.49238	0.18371
2,4-dioxo 6,7-di-propynyl 8-ethyl 1,2,3,4-tetrahydropteridine (10)	-907.34615	0.25883
6,7-di-methyl 1-hydro 5,8,9-tri-dehydro isoalloxazine (11)	-829.02990	0.22830
9-dehydro 6,7-di-methyl 1-hydro isoalloxazine (12)	-830.35155	0.22671
1,9-didehydro 6,7-di-methyl isoalloxazine^{-} (13)	-829.80088	0.21217
Mg.porphin (14)	-1185.12250	0.29262
Mg.porphin.4CO (15)	-1636.80888	0.31847
Mg.porphin.(CO-)$_4$ (16)	-1636.96846	0.32040
Mg.porphin.(CO-)$_3$.C(-OH).CN (17)	-1730.20912	0.35688
Mg.porphin.H.C(-OH)$_4$.CH$_2$NH$_2$. (18)	-1734.81264	0.45400
D-ribitylamine.(19)	-552.30769	0.22547
D-ribitylamine^{+} (20)	-552.67396	0.23064
D-riboflavin (21)	-1326.27656	0.40325
6,7-di-methyl 9-ethyl isoalloxazine (22)	-908.66060	0.28772

1,10 dihydro 6,7-di-methyl 9-ethyl isoalloxazine (23)	-909.82437	0.31290
$CH_3CH_2NH_3^+$	-135.04152	0.11511
CO	-113.02122	0.00566
$OH^·$	-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 Riboflavin

The overall stoichiometry to form the riboflavin is as follows,

$$2\ CH_3\text{-}C \equiv C\text{-}H + 2\ N \equiv C - C \equiv N + 6\ CO + 7H_2 + HCN \rightarrow C_{17}H_{20}N_4O_6 + NH_3 \quad (1)$$

Riboflavin, Figure 1.

$$\Delta H = -0.35518\ h$$

The enthalpy change is negative indicating that this may be the energetically favorable route to the initial formation of the riboflavin. The intermediates by which these stoichiometric reactions may have occurred are as follows:

The first sequence involves the formation of the isoalloxazine anion as,

$$2\ CH_3\text{-}C \equiv C\text{-}H + 2\ N \equiv C - C \equiv N + 2\ CO + H_2 \rightarrow C_{12}H_9N_4O_2^- + H^+ \quad (2)$$

isoalloxazine$^-$

$$\Delta H = 0.25355\ h$$

The second sequence involves the formation of D-ribitylamine$^+$, where the Mg.porphin catalyst is required to give the D-ribose configuration, [16].

$$4\ CO + HCN + 6\ H_2 + H^+ \rightarrow C_5H_{14}NO_4^+ \quad (3)$$

D-riboseamine

$$\Delta H = -0.45052\ h$$

This is followed by the bonding of the isoalloxazine anion and D-ribitylamine cation in a Sn2 substitution reaction to give a neutral D-riboflavin molecule as,

$$\text{isoalloxazine}^- + \text{D-ribitylamine}^+ \rightarrow \text{D-riboflavin} + NH_3. \quad (4)$$

$$\Delta H = -0.15821\ h$$

Molecules are numbered consecutively.
Subsections depict alternatives in the sequence of the reaction mechanism.
A standard numbering of the atoms in riboflavin is shown in Figure 1, [3], [17].

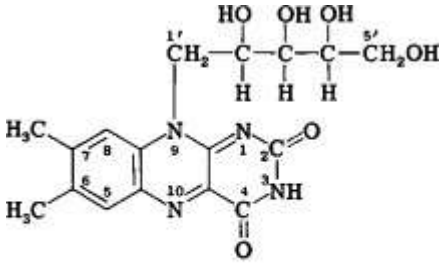


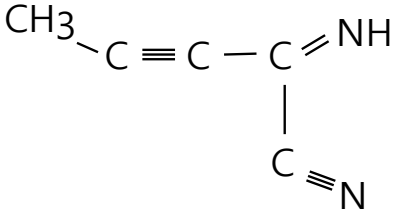
Fig. 1: Riboflavin

3.3 The Formation of 4-imido but-2-yn cyanide

The polarization in the gases propyne and cyanogen suggests a gas phase condensation reaction may occur as,

$$CH_3\text{-}C \equiv C\text{-}H + N \equiv C\text{-}C \equiv N \rightarrow \quad (5)$$

(1) (2)



4-imido but-2-yn cyanide (3)

$$\Delta H = 0.01693\ h$$
$$\Delta G = 0.00115\ h$$

The reaction appears marginally feasible.
The potential energy surface for the transfer reaction between propyne and cyanogen is given in Figure 2.

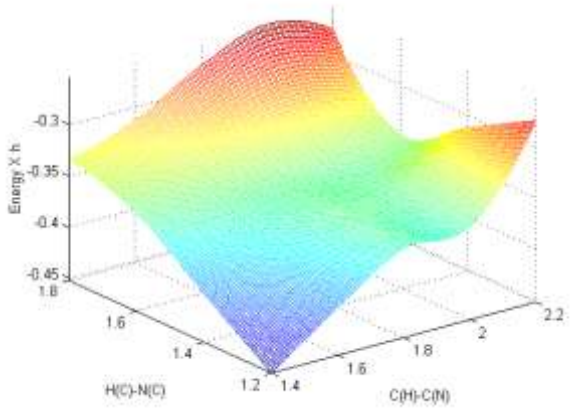


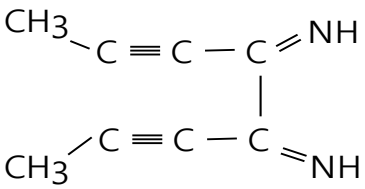
Fig. 2: The potential energy diagram for the formation of 4-imido but-2-yn cyanide where the x-axis is C(C≡) –C(CN) and the y-axis is the H(N)-C(C≡) bond extension. The reactants are at (2.5,1.8), the 4-imido but-2-yn cyanide at (1.4,1.2), and the saddle point at (1.7,1.5). The energy = -300.0 + X h.

The activation energy for the forward reaction was calculated as 0.120 h and 0.102 for the reverse reaction.

3.4 The Formation of 4,5-di-imido octan-2,6-diyne

Another molecule of propyne may also be added in a further equilibrium reaction as shown,

CH_3-C ≡ C- H + CH_3-C≡ C-C(=NH)-C≡N →
(1) (3) (6)



4,5-di-imido octan-2,6-diyne. (4)

$$\Delta H = -0.01691 \text{ h}$$

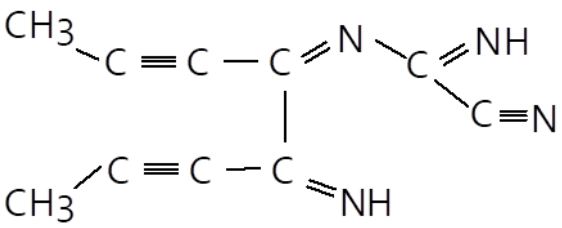
The activation energy for the second addition was 0.100 h and 0.101 for the reverse reaction. The combined energy for the addition of two molecules of propyne to cyanogen is then,

$$\Delta H = 0.00002 \text{ h}$$

3.5 The Formation of 4- (2-cyano 1-methanimido)-imido-5-imido octan-2,6-diyne

A further condensation may involve the reaction of the cyanogen with 4,5-di-imido octan-2,6-diyne as,

4,5-di-imido octan-2,6-diyne + cyanogen →
(7)



4- (2-cyano 1-methanimido)-imido-5-imido octan-2,6-diyne (5)

$$\Delta H = -0.01189 \text{ h}$$
$$\Delta G = 0.002856 \text{ h}$$

The addition reaction is favorable and treated as a transfer reaction followed by ring closure. A 1:4 addition reaction would also suffice. The potential energy surface for the first addition is given in Figure 3.

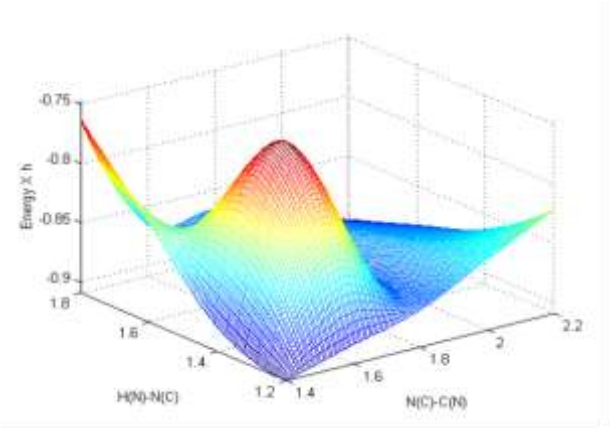


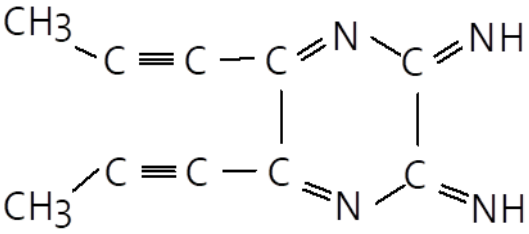
Fig. 3: Potential energy surface for the addition of cyanogen to 4,5-di-imido octan-2,6-diyne. The x-axis is the N-C bond formation, the y-axis is the H-N bond formation. The reactants are at (2.2,1.6), the product at (1.4,1.2), and the saddle point at (1.8,1.2). The energy is -600.0 +X h.

The activation energy for the reaction was calculated as 0.120 h for the condensation and 0.120 h for the reverse reaction.

3.6 The Formation of 5.6-dipropynyl 1,4-pyrazine

The 4- (2-cyano 1-methanimido)-imido-5-imido octan-2,6-diyne may cyclicise to form a pyrazine derivative as,

4- (2-cyano 1-methanimido)-imido-5-imido octan-2,6-diyne → (8)



2,3-di-imido 5.6-dipropynyl 1,4-pyrazine (6)

$$\Delta H = 0.00625 \text{ h}$$

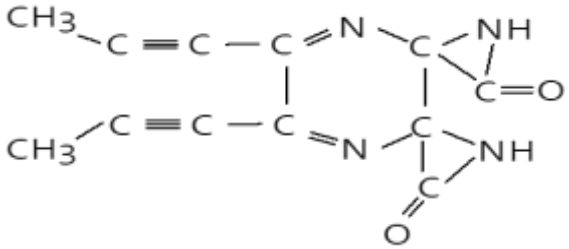
The cyclization is favorable with an activation energy of 0.006 h. The combined enthalpy change for the addition of the cyanogen molecule is then,

$$\Delta H = -0.00564 \text{ h}$$

3.7 The Formation of 2,3-di-aziridon-2yl 5.6-dipropynyl 1,4-pyrazine

The di-imido groups of the pyrazine derivative are prone to reaction with two molecules of carbon monoxide to form aziridone ring substituents as,

2,3-di-imido 5.6-dipropynyl 1,4-pyrazine + 2 CO → (9)



2,3-di-aziridon-2yl 5.6-dipropynyl 1,4-pyrazine. (7)

$$\Delta H = 0.06614 \text{ h}$$

The enthalpy change for the first addition was calculated as,

$$\Delta H = 0.027 \text{ h}$$

where the activation energy was the same as the enthalpy change, [18].

The enthalpy change for the second addition was calculated as,

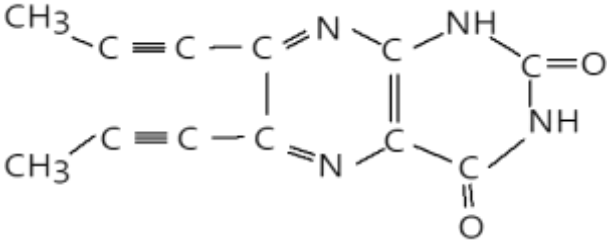
$$\Delta H = 0.031 \text{ h}$$

where the activation energy was the same as the enthalpy change.

3.8 The formation 2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine

The 2,3-di-aziridon-2yl 5.6-dipropynyl 1,4-pyrazine may rearrange bonding to give a pteridine derivative, [3], as,

2,3-di-aziridon-2yl 5.6-dipropynyl 1,4-pyrazine → (10)



2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine (8)

$$\Delta H = -0.19190 \text{ h}$$

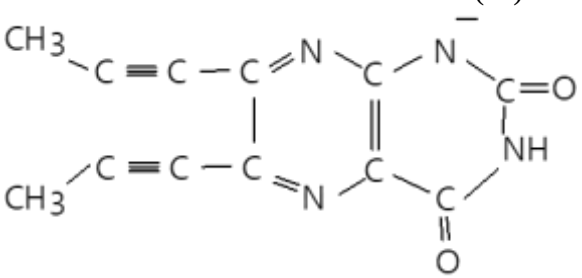
The activation energy for the rearrangement was 0.238 h and for the reverse 0.316 h.

The molecule may experience keto–enol isomerization, [3].

3.8.1 The formation of 1-dehydro 2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine$^-$

At this stage in the mechanism the molecule may ionize in the presence of hydroxyl anion as,

2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine + OH^- → H_2O + (11)



1-dehydro 2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine$^-$ (9)

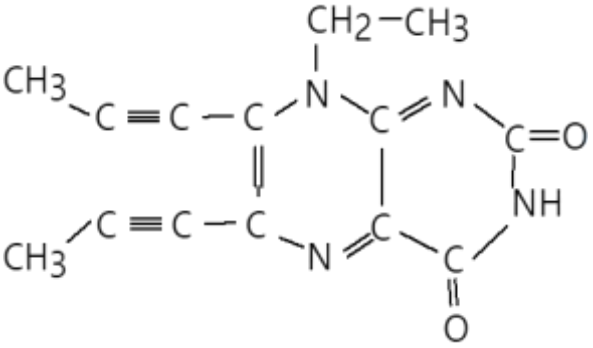
$$\Delta H = -0.13776 \text{ h}$$

A further reaction could occur at this point with D-ribitylamine.

3.8.2 The formation of 2,4-dioxo 6,7-di-propynyl 8-ethyl 1,2,3,4-tetrahydropteridine

At this point in the reaction sequence the pteridine anion may react with an alkyl ammonium compound in a classical Sn2, [19], substitution reaction. To reduce computing time this is first computed here using ethylamine cation as,

1-dehydro 2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine$^-$ + $CH_3CH_2NH_3^+ \rightarrow NH_3$ + (12)



2,4-dioxo 6,7-di-propynyl 8-ethyl 1,2,3,4-tetrahydropteridine (10)

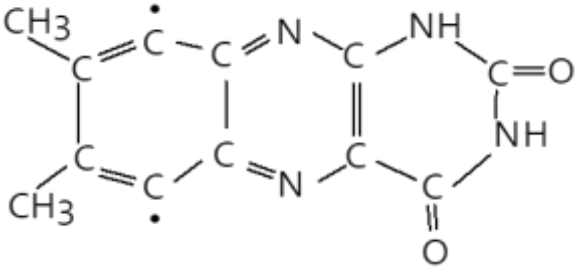
ΔH = -0.17380 h

The activation energy was calculated as -0.086 h, and for the reverse reaction 0.081 h.

3.9 The formation of 6,7-di-methyl 1-hydro 5,8,9-tri-dehydro isoalloxazine

The 2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine may cyclize as,

2,4-dioxo 6,7-di-propynyl -1,2,3,4-tetrahydropteridine → (13)



6,7-di-methyl 1-hydro 5,8,9-tri-dehydro isoalloxazine (11)

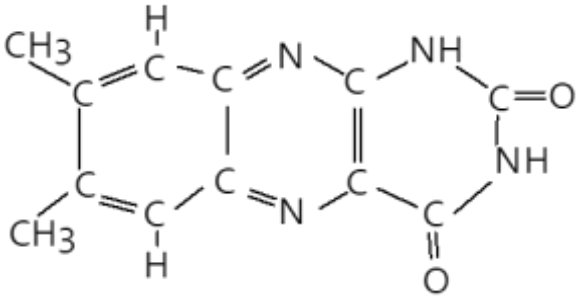
ΔH = 0.03554 h

The activation energy for the ring closure was 0.130 h and .0.129 h for the reverse.

3.10 The formation of 9-dehydro 6,7-di-methyl 1-hydro isoalloxazine

The 6,7-di-methyl 1-hydro 5,8,9-tri-dehydro isoalloxazine may react with hydrogen radicals or molecular hydrogen as,

6,7-di-methyl 1-hydro 5,8,9-tri-dehydro isoalloxazine + $H_2 \rightarrow$ (14)



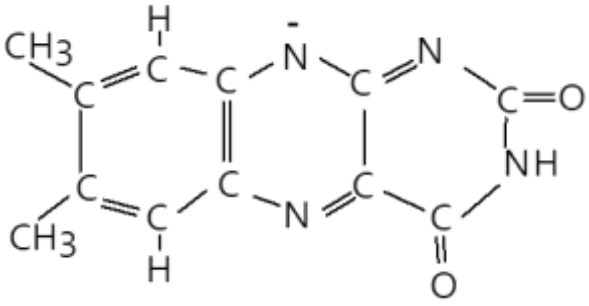
9-dehydro 6,7-di-methyl 1-hydro isoalloxazine (12)

ΔH = -0.18835 h

3.11 The formation of 6,7-di-methyl 1,9-didehydro isoalloxazine

The ionization of 9-dehydro 6,7-di-methyl 1-hydro isoalloxazine may be represented as,

9-dehydro 6,7-di-methyl 1-hydro isoalloxazine + $OH^- \rightarrow H_2O$ + (15)



1,9-didehydro 6,7-di-methyl isoalloxazine$^-$ (13)

ΔH = -0.13340 h

The charges on nitrogen atoms 1,3,9 and 10 were -0.74, -0.92, -0.66, and -0.53, respectively.

Before this 6,7-di-methyl 1,9-didehydro isoalloxazine nucleophile may act as a nucleophilic reagent and react with D-ribitylamine $^+$ the D-ribitylamine needs to be synthesized.

3.12 The formation of D-ribitylamine

To form the steric D-ribose sugar requires a catalyst Mg.porphin or Fe.porphin, [20], [21], where the magnetic vector of radiation, or the presence of a

magnetic field within the catalyst can induce a directed charge polarization, [16].

3.13 The formation of Mg.porphin.4CO

The carbon monoxide may react with the catalyst Mg.porphin to produce a magnesium bound or nitogen bound adduct where the latter is of higher energy induced by radiation, [16]. The products may be represented as,

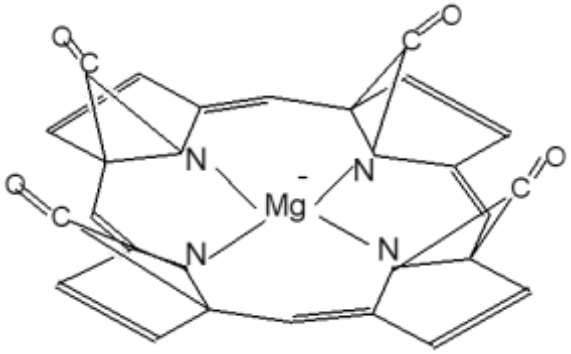
Mg.pprphin + CO → Mg.CO.porphin

and

Mg.pprphin + CO → Mg.porphin.CO

To form the required sugar requires the formation of four carbon monoxide adducts to be added in separate additions to give a tetra-dentate complex, represented as,

Mg.porphin + 4CO →
(14) (16)

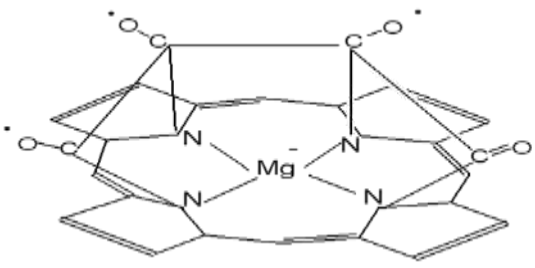


Mg.porphin.4CO (15)

$\Delta H = 0.40170$ h

This complex may then be excited to weakly bond as a free radical complex as,

Mg.porphin.4CO → (17)



Mg.porphin.$(CO\text{-})_4$ (16)

$\Delta H = -0.15786$ h

The net charge on the adducts for Fe.porphin. $(CO\text{-})_4$ is 0.217, whilst that of the Fe.porphin ring atoms is -0.217

Alternate bonding during excitation is expected to yield some D-erythrose and D-threose isomers. The bonded structure used for the calculation of the surface potential energy for the formation of the analogous D-ribose is given in Figure 4.

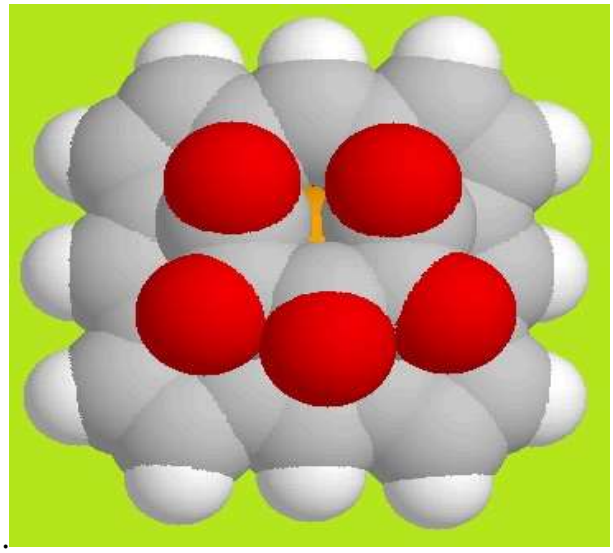


Fig. 4: The Fe.porphin.$(CO\text{-})_5$.structure used for the analogous potential energy surface

An isovalue through the potential energy surface for the potential energy surface for Fe.porphin.$(CO\text{-})_5$ is shown in Figure 5 displaying charge asymmetry induced by the magnetic field in the molecule.

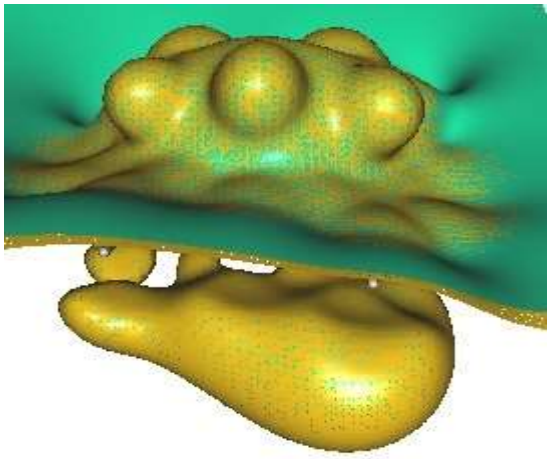


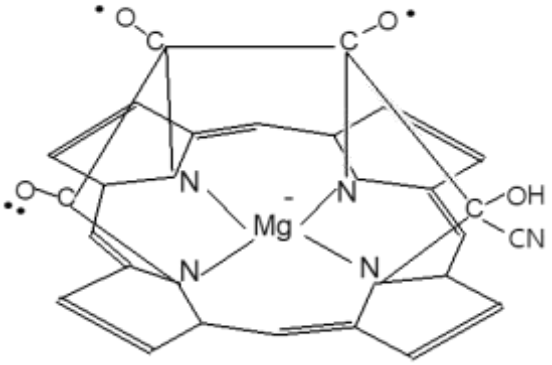
Fig. 5: An isosurface for the analogous potential energy surface of Fe.porphin.$(CO\text{-})_5$. Adduct - positive, porphin ring –negative

The potential energy surfaces depict an asymmetric charge distribution when the molecule mounts a diamagnetic response to the presence of a magnetic vector in the molecule arising from photochemical excitation where the electric vector is in plane and the magnetic vector perpendicular to the porphin plane, [16], or from the presence of the a coordinated ferrous atom in the porphin molecule. This charge surge causes the bonded carbon monoxide adducts to bond in an anticlockwise direction when viewed from above, to pick up a proton, or react further to give higher sugars.

3.14 The formation of Mg.porphin.$(CO\text{-})_4$.H-CN

The asymmetric charge directs the reaction with a hydrogen cyanide molecule to be as shown.

$Mg.porphin.(CO\text{-})_4 + H\text{-}CN \rightarrow$ (18)



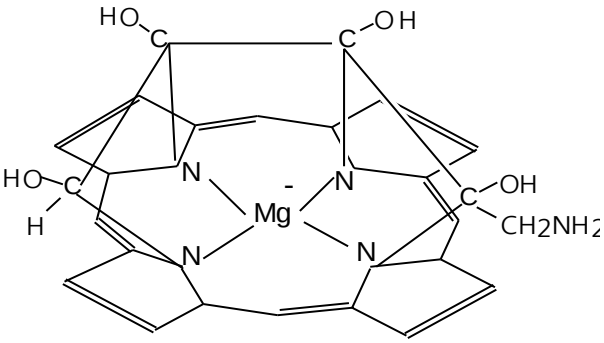
$Mg.porphin.(CO\text{-})_3.C(\text{-}OH).CN$ (17)

$\Delta H = -0.06343$ h

3.15 The formation of Mg.porphin.H.C(-OH)$_4$. CH_2NH_2.

Further hydrogenation, [22], forms the D-ribose hydroxyl groups as,

$Mg.porphin.(CO\text{-})_3.C(OH)\text{-}CN + 4H_2 \rightarrow$ (19)



$Mg.porphin.H.C(\text{-}OH)_4.CH_2NH_2$. (18)

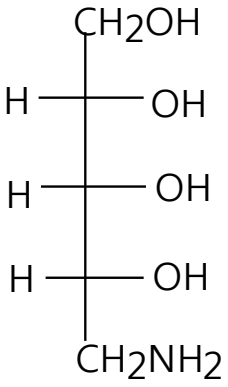
$\Delta H = 0.02178$ h

3.16 The formation of D-ribitylamine

The $Mg.porphin.H.C(\text{-}OH)_4.CH_2NH_2$ may be fully reduced with hydrogen molecules or free radicals to release the catalyst as,

$Mg.porphin.H.C(\text{-}OH)_4.CH_2NH_2 + 2H_2 \rightarrow$

$\rightarrow$ Mg.porphin + (20)



. D-ribitylamine.(19)

$\Delta H = -0.29106$ h

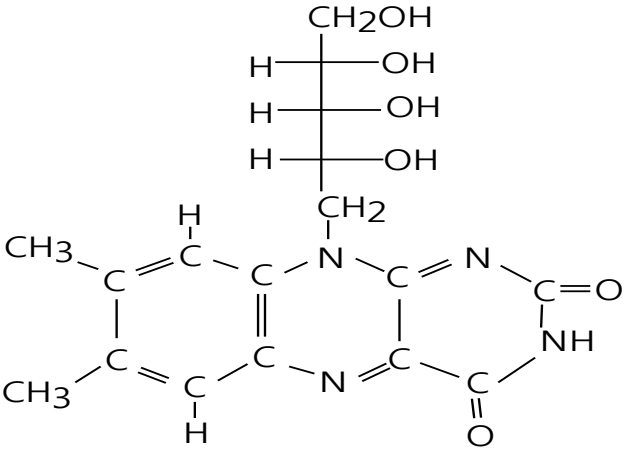
The molecule may be further protonated as,

$D\text{-ribitylamine.} + H^+ \rightarrow D\text{-ribitylamine}^+.$ (20) (21)

$\Delta H = -0.36167$ h

3.17 The formation of D-riboflavin

The isoalloxazine anion and the D-ribityl cation may react as, $isoalloxazine^-$ + $D\text{-ribitylamine}^+ \rightarrow$ D-riboflavin + NH_3 (22)



D-riboflavin (21)

$\Delta H = -0.15821$ h

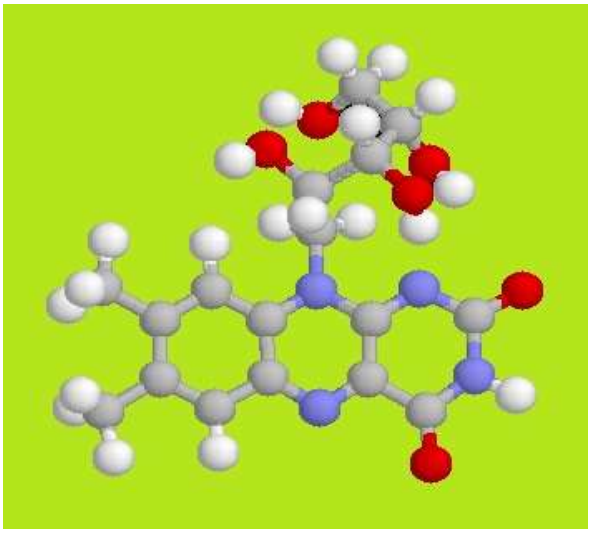
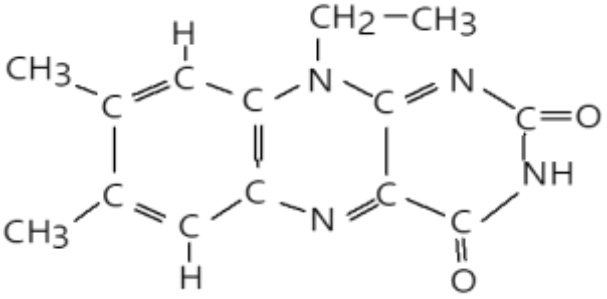


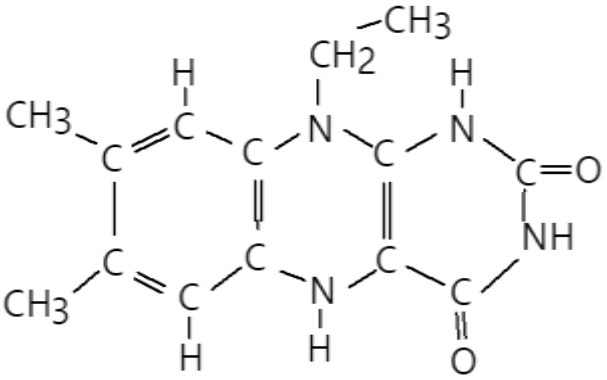
Fig. 6: D-riboflavin

3.17.1 The formation of 6,7-di-methyl 9-ethyl 1,10 dihydro isoalloxazine

The riboflavin molecule may carry hydrogen for hydrogenation reactions at the N1 and N10 positions as illustrated here with a reduced 9-substituent to reduce computing time as,



6,7-di-methyl 9-ethyl isoalloxazine + H_2 →
(22) (23)



1,10-dihydro 6,7-di-methyl 9-ethyl isoalloxazine (23)

$\Delta H = -0.00642$ h

4 Conclusion

The gaseous reactants used in this proposed synthesis have all been found or inferred as being present in interstellar space, [23], [24], and many are found on individual moons and planets of our solar system, [25]. The catalyst Mg.porphin has also been cited as from the time of photosynthesis, [26].

The photochemically catalyzed addition reactions of the simple gases propyne, cyanogen, and hydrogen may plausibly form the isoalloxazine molecular structure prone to keto-enol isomerization, whilst the photochemically activated surface catalysed oligomerization of carbon monoxide followed by hydrogenation may form the steric selected D-ribityl sugar. The anion and cation may then participate in a Sn2 substitution reaction to form the vitamin., The reactions do appear to be thermodynamically viable with acceptable activation energies. If the concentrations of the gases were very low, the time for reactions, which could be astronomical, should have allowed some product from the synthesis to cover the planet at the same time as peptides and proteins were being formed, [27], as implied and inevitable according to the immutable laws of chemistry. The existence of this molecule as an enzyme prosthetic group does suggest it is of extreme antiquity.

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

Acknowledgement:
Appreciation is expressed to Gaussian Inc.

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Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

The author contributed in the present research, at all stages from the formulation of the problem to the final findings and solution.

Sources of Funding for Research Presented in a Scientific Article or Scientific Article Itself

No funding was received for conducting this study.

Conflict of Interest

The authors have no conflict of interest to declare.