A Computational Study of a Prebiotic Synthesis of L-Asparagine, L-Aspartic Acid, L-Glutamine and L-Glutamic Acid

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Abstract: - The magnesium ion metalloporphyrin complex is shown to bind the ligands cyanoacetylene and 2-cyanoethanimine in weak van der Waals complexes on the metal site. Further reaction of the bound cyanoacetylene with ammonia gives an amine that easily transforms to an aziridine derivative, and ultimately an imine bound to the catalyst. When carbon monoxide is also bound to the complex as a high energy compound whose particular structure has been dictated by the magnetic vector of the exciting radiation, reaction occurs to give a substituted aziridine-2one that may easily hydrolyse to the zwitterionic form of the amino acids L-asparagine and L-aspartic acid.
Dicyano derivatives of acetylene such as dicyano acetylene, dicyano ethene and dicyano ethane when partially reduced to the corresponding imines also form weak van der Waals charge transfer complexes with the catalyst, Mg.porphin, that react in a similar sequence of reactions to give L-glutamine and ultimately L-glutamic 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, and with acceptable activation energies.

Key-Words: - Prebiotic photochemical synthesis, L-asparagine, L-aspartic acid, L-glutamine, L-glutamic acid.

1 Introduction

The amide L-asparagine (Asn,N) and L-aspartic acid (Asp,D), L-amino succinic acid, are non-essential amino acids [1], that occur naturally as the L-isomer [2] and are present in many proteins such as insulin, myosin, and ovalbumin [3]. L-asparagine was discovered in asparagus and is abundant in peas, soya beans and vetch [1]. The enzyme asparaginase converts it into ammonia and aspartic acid [4]. It is easily hydrolysed by acid or base to aspartic acid [1]. In biological systems the equilibrium,

$$\text{fumarate} + NH_3 \leftrightarrow \text{aspartate}$$

is catalyzed in favour of only the L-amino acid by the enzyme aspartase, and its configuration has been systematized by its relationship to L-malic acid [1].
Aspartic acid has a side-chain carboxyl pK_a of 3.65, and an α-COOH pK_a, 1.88 and an α-NH_2 pK_a 9.60 [1-2,5].
The catabolic pathway for asparagine or aspartic acid involves transamination [1]. The biosynthesis is documented [6]. These amino acids are involved in transcription and in the aspartic proteolytic enzymes, [7].
The amide L-glutamine (Gln,Q) and L-glutamic acid (Glu,E), L-amino glutaric acid, are also non-essential amino acids [1], that occur naturally as the L-isomer [2] and are present in plant storage proteins such as wheat gliadin and corn zein [1] and edestin from hemp seed [2], haemoglobin [8], ovalbumin [2], and the growth factor, pteroyl glutamic acid [9].
Biochemically, glutamic acid is directly involved in the formation of glutamine from α-ketoglutaric acid and ammonia, in glutathione formation, the nitrogen cycle, nitrogen metabolism, oxidative deamination and transamination, and provides a source of nitrogen in the synthesis of pyrimidines and purines [5].
At neutral pH both glutamine and glutamic acid are present in solution as zwitterions. Glutamic acid has a side-chain carboxyl pK_a of 4.25, and an α-COOH pK_a, 2.19 and an α-NH_2 pK_a 9.67 [1-2]. L-glutamine has corresponding pK_a's of 2.17 and 9.13 [1]..
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 [1,11] implying the presence of concentrations of carbon monoxide, ammonia, water and hydrogen. It is also supposed that alkynes such as cyanoacetylene were present as found on Titan, a moon of Saturn [12]. A major determinant

for the formation of prebiotic asparagine and aspartic acid may have been the favourable concentration of cynoacetylene that has been found in experiments on mixtures of gases of alkyne and nitrogen [11]. The presence of 2-cyanoethanimine formed by the partial reduction of dicyanomethane, may have also been a reactant It has also been demonstrated that porphin may act as a catalyst for the formation of sugars [13] and polyenes [14], and amino acids [15-19].

This paper proposes a model for the catalytic photochemically activated formation of L-asparagine and L-aspartic acid from the gases, cyanoacetylene (or 2-cyanoethanimine), and L-glutamine and L-glutamic acid from 1,2-dicyanoacetylene (or 3-propanimine), ammonia, carbon monoxide, hydrogen, and the catalyst magnesium porphin..

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 L-asparagine, L-aspartic acid, L-glutamine and L-glutamic 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 GAUSSIAN03 [20] commercial package. The standard calculations at the HF and MP2 levels including zero-point energy corrections at the Hartree Fock level, [21], together with scaling [22], using the same basis set, 6-31G*. are as previously published [10]. 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 [21], 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 [20].

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

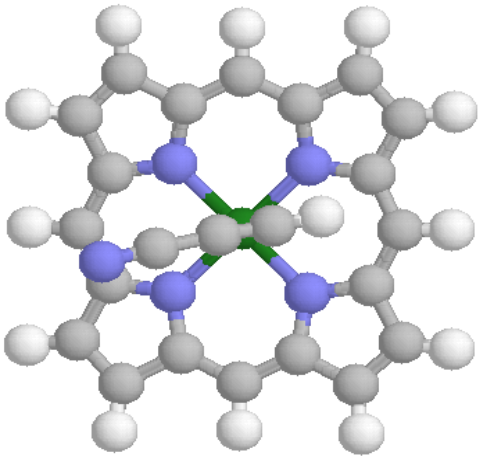
Charges are in units of the electronic charge.

3 Problem Solution

3.1 Total Energies (hartrees)

Cyanoacetylene may chelate with the magnesium ion of magnesium porphin, which is here taken as a possible catalyst, to form an in-plane charge transfer complex where the charge on the ligand is positive, 0.02. and the charge on the porphin molecule is negative. The enthalpy of formation of the van der Waals complex is small but it appears stable.

Mg.porphin + H-C≡C-CN →
(1) (2) [1]



Mg.H-C≡C-CN.porphin (3)

ΔH = -0.02164 h

Apart from the negative formal charge on the alkyne methine carbon atom (-0.39) cyanoacetylene also has a formal negative charge (-0.46) on the nitrogen atom of the cyanide group. When the magnesium ion binds the nitrogen of the cyanide group with the catalyst, Mg.porphin, to form an axially oriented complex the formal positive charge on the ligand is larger, (0.08), as follows,

Mg.porphin + NC-C≡C-H → Mg.NC-C≡C-H.porphin
(1) (2) (4) [2]

ΔH = -0.02471 h

Although the enthalpy changes are comparable, only the former product is used in this synthesis.

This is the first reactant required in the synthesis.

3.2 The asymmetric induction of chirality

Mg.porphin also forms a stable complex[13] with carbon monoxide in which the carbon monoxide is bonded to the magnesium ion, as shown,

Mg.porphin + CO → Mg.CO.porphin

(1) (5) [3]

$$\Delta H_{(HF)} = -0.00919 \text{ h}$$

This is the low energy complex [13]. When this complex is photchemically activted, an in-plane electronic transition occurs in which the HOMO may be excited to the LUMO [13]. If the magnetic vector of the radiation is directed perpendicularly upward from the ring when viewed from above, the energy levels of the HOMO and LUMO are each split according to the Zeeman effect [23] and the adduct may dissociate, and rise in height above the ring. The first excitation energy (0.21 h) is greater than the activation energy (0.19668 h) and much greater than the bonding energy (-0.02164 h) [13]. The system of conjugated bonds in porphin has been approximated to the particle on a ring quantum mechanical problem [24]. In this model the molecule is described as a cyclic system [25] where the removal of the degeneracy of the orbitals by the magnetic field allows the contributing mesomeric forms [26] to have different energies, as shown in Fig.1.

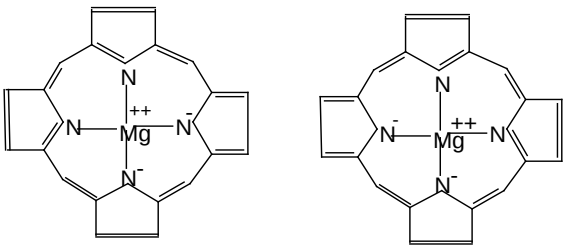


Fig.1. Mesomeric forms of Mg.porphin in the presence of a magnetic field pointing perpendicularly upwards from the ring towards the observer.

Four transitions may occur[23] of which two are allowed by the selection rules [27]. As the molecule is normally diamagnetic [28] the highest energy HOMO orbital should correspond to that shown as Fig.1(1) . It is postulated that the CO group is able to move through a transition state to the porphin ring where it forms an excited, but stable bridged aziridine-2one ring [13,29-30] at a pyrrole unit with this isomer, as shown, Fig.2(1)

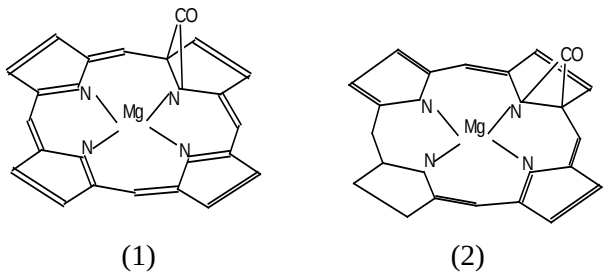


Fig.2. Isomers of Mg.porphin.CO

This is a higher energy charge transfer complex, where a high proportion of the photochemical energy has been conserved as chemical energy. If the magnetic field reverses the positively charged adduct is compressed down on the ring and less liable to reaction. If the unfavourabe complex Fig.2(2) is formed from atmospherically activated carbon monoxide, then further excitation may lift the adduct from the periphery of the ring and convert it to the more favourable orientation for assymmetric induction. The activation energy required to convert the forms Fig.2(1) to Fig.2(2) is < 0.11 h.

This is also involved in the proposed synthesis, as shown later. The formation requires photochemical activation,. The enthalpy of formation is positive.

Mg.porphin + CO → Mg.porphin.CO
(1) (6)
ΔH = 0.21136 h [4]

Mg.CO.porphin → Mg.porphin.CO
(5) (6) [5]
ΔH = 0.20106 h

These are the reactants that will be used in the synthesis of the amino acids, asparagine and aspartic acid.

The total energies and zero point energies for the HF and MP2/6-31G* equilibrium geometries for some of these stable molecules are given 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
Mg.porphin (1)	-1185.12250	0.29262
cyanoacetylene(2)	-169.07910	0.02989
Mg.H-C≡C-CN.porphin (3)	-1354.21912	0.31789
Mg.NC-C≡C-H.porphin (4)	-1354.22176	0.31740
Mg.CO.porphin (5)	-1298.13452	0.29942

Mg.porphin.CO (6)	-1297.93784	0.30434
L-aspartic acid (non-zwitterion)(7)	510.85516	0.13399
Mg-1,2-cyano-2-amino ethyn-1yl.porphin**.** (8)	-1410.53978	0.36149
Mg.1,3-cyano 1H aziridin-2-yl.porphin (9)	-1410.55992	0.36255
Mg.1,2-cyanoethanimin-1-yl.porphin (10)	-1410.65244	0.36226
2-cyanoethanimine (11)	-225.49280	0.07339
Mg.1,2-cyanoethanimin-1-yl.porphin.CO (12)	-1523.63188	0.37217
NC-CH_2-CN (13)	-224.33204	0.04845
Mg.1,(2-cyanomethyl) aziridine-3-one-1-yl.porphin. (14)	-1523.65177	0.37250
L-asparagine (15)	-491.00992	0.14656
H-C≡C-H	-77.06679	0.02945
CH_4	-40.33255	0.04777
HCN	-93.15894	0.01799
CO	-113.02122	0.00556
H_2O	-76.19685	0.02298
NH_3	-56.35421	0.03700
H_3^+	-1.29643	0.02210
H_2	-1.14414	0.01059

3.3 The overall stoichiometry for the formation of L-aspartic acid.

Although Mg.porphin is here taken as the catalyst for the reaction, the overall stoichiometry to form the amino acid, L-aspartic acid is as follows,

$$H\text{-}C{\equiv}C\text{-}CN + CO + 3H_2O \rightarrow C_4H_7NO_4 \quad (7) \quad [6]$$

Fig.2.aspartic acid (non-zwitterion)

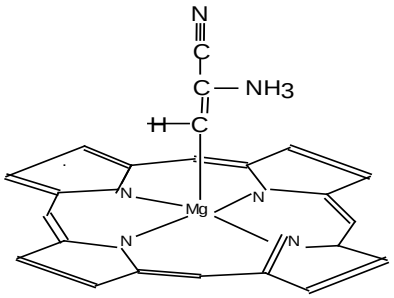
$\Delta H = -0.13794$ h

The enthalpy change is negative indicating that this may be the energetically favourable route to the initial formation of the amino acid. The intermediates by which this stoichiometric reaction may have occurred are as follows:

3.4 The formation of Mg-1,2-cyano-2-amino ethyn-1yl.porphin.

The Mg-1,2-cyanoethyn-1yl.porphin may react with ammonia, as shown,

Mg.H-C≡C-CN.porphin + NH_3 → (3) [7]



Mg-1,2-cyano-2-amino ethyn-1yl.porphin**.** (8)

The enthalpy change is not favourable as this is the rate determining step in the synthesis.

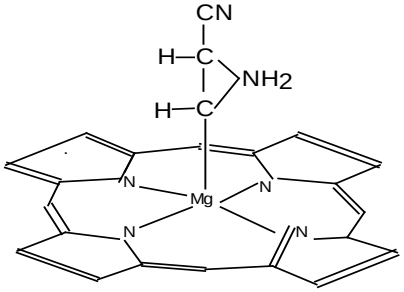
$$\Delta H = 0.03943 \text{ h}$$

The activation energies for the forward and reverse reactions were calculated as 0.034 h and 0.004 h, respectively.

3.5 The formation of Mg.1,3-cyano 1H aziridin-2-yl.porphin

The Mg-1,2-cyano-2-amino ethyn-1yl.porphin**.** may cyclise to an aziridine derivative during being activated to transfer a hydrogen atom. The enthalpy change is favorable.

Mg-1,2-cyano-2-amino ethyn-1yl.porphin →



Mg.1,3-cyano 1H aziridin-2-yl.porphin (9) [8]

$\Delta H = -0.01920$ h

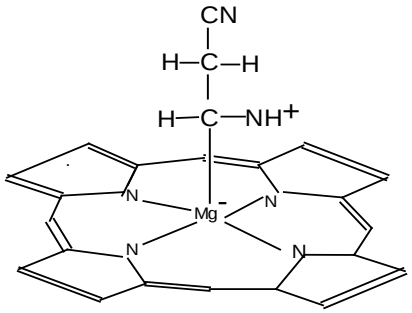
The activation energy to form the carbon-hydrogen bond was found to be, 0.091 h, whilst the energy to restore the nitrogen-hydrogen bond was 0.103 h. The aziridine ring forms during this first hydrogen transfer.

3.6 The formation of Mg.1,2-cyanoethanimin-1-yl.porphin

With only moderate activation energy a second hydrogen atom may be transferred from the protonated

amino group to form the second carbon-hydrogen bond and opening the aziridine ring [15], as shown.

Mg.1,3-cyano 1H aziridin-2-yl.porphin
(9) →



Mg.1,2-cyanoethanimin-1-yl.porphin (10) [9]

$\Delta H = -0.09278$ h

The activation energy to open the ring was calculated as 0.127 h, whilst that to close it was 0.235 h. These values are comparable to those previously found for the formation of the amino acids serine and threonine [15]. At the transition state the metal bonding changes from Mg-C to Mg-N. The imine is expected to dissociate to a minor extent with a small vapour pressure, but this requires a small activation energy according to the equation,

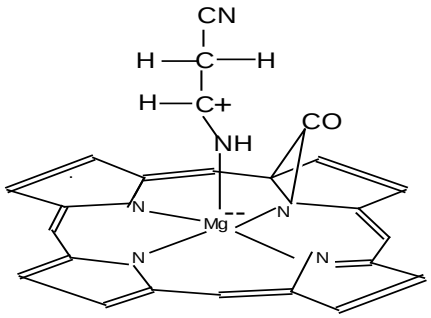
Mg.1,2-cyanoethanimin-1-yl.porphin → Mg.porphin + 2-cyanoethanimine
(11) [10]

$\Delta H = 0.04048$ h

3.7 The formation of Mg.1,2-cyanoethanimin-1-yl.porphin.CO

For the correct formation of the L-isomer the 2-cyano ethanimine needs to chelate to the magnesium ion on a Mg.porphin which has already obtained the correct orientation of a bound carbon monoxide molecule [13], as shown,

Mg.porphin.CO + 2-cyanoethanimine
(6) (11) →



Mg.1,2-cyanoethanimin-1-yl.porphin.CO (12) [11]

$\Delta H = -0.20619$ h

The enthalpy change is favourable and the activation energy to form van der Waals complexes is usually not significant if they are spontaneous.
The 2-cyanoethanimine may have also arisen from the reduction of volatile atmospheric dicyanomethane,

$NC\text{-}CH_2\text{-}CN + H_2 \rightarrow NC\text{-}CH_2\text{-}CH{=}NH$
(13) (11) [12]

$\Delta H = -0.00385$ h

formed from methane and hydrogen cyanide,

$CH_4 + 2HCN \rightarrow CH_2(CN)_2 + 2H_2$
(13) [13]

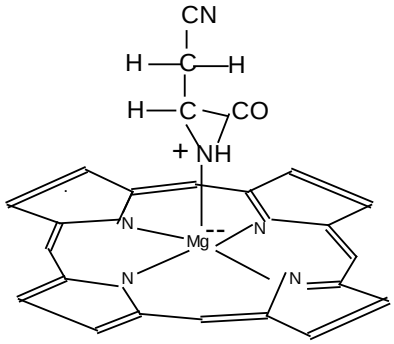
$\Delta H = 0.01755$ h

3.8 The formation of Mg.1,(2-cyanomethyl) aziridine-3-one-1-yl.porphin.

The Mg.1,2-cyanoethanimin-1-yl.porphin.CO may easily rearrange to form Mg.1,(2-cyanomethyl) aziridine-3-one-1-yl.porphin with an activation energy of 0.144 h and a ring dissociation energy of 0.150 h. The enthalpy change is favourable.

$\Delta H = -0.01959$ h

The Mg.1,2-cyanoethanimin-1-yl.porphin.CO
(12) →



Mg.1,(2-cyanomethyl) aziridine-3-one-1-yl.porphin. (14) [14]

3.9 The formation L-asparagine and L-aspartate.

Hydrolysis in the reducing environment of the complex, is here depicted as releasing from the catalyst either the amide, asparagine, or with further hydrolysis.the undissociated aspartic acid acid, Fig.2. Further formation of the zwitterions may occur.

Mg.1,(2-cyanomethyl) aziridine-3-one-1-yl.porphin. + **2**H_2O → Mg.porphin + L-asparagine (15) [15]

$\Delta H = -0.06892$ h

Mg.1,(2-cyanomethyl) aziridine-3-one-1-yl.porphin. + **3**H_2O → Mg.porphin + L-aspartic acid [16]

$\Delta H = -0.06982$ h

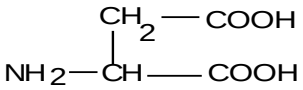


Fig.2 L-aspartic acid (non zwitterion) (7)

4. The reactants to form L-glutamine and L-glutamic acid.

Photolysis of molecules present in the atmosphere of Titan, such as acetylene [31] and of cyanoacetylene [32] indicate the formation of a small concentration of dicyanoacetylene which is also proposed in a simulation of Titan's atmospheric chemistry [12].
The calculated enthalpy change in the substitution reactions of acetylene and hydrogen cyanide indicate small marginally favourable enthalpy changes, that would be expected to occur by free radical and ionic reactions in the atmosphere containing acetylene and hydrogen cyanide [33].

$H\text{-}C\equiv C\text{-}H + H\text{-}CN \rightarrow NC\text{-}C\equiv C\text{-}H + H_2$ [17]

$\Delta H = -0.00370$ h

$H\text{-}C\equiv C\text{-}H + 2\ H\text{-}CN \rightarrow NC\text{-}C\equiv C\text{-}CN + 2\ H_2$ (16) [18]

$\Delta H = -0.00381$ h

However, the addition reactions of acetylene and hydrogen cyanide produce large enthalpy changes indicating the probable presence of these molecules although their detection may be more difficult if there is zero permanent dipole moment.

$H\text{-}C\equiv C\text{-}H + 2\ H\text{-}CN \rightarrow NC\text{-}HC=CH\text{-}CN + H_2$ (17) (trans) [19]

$\Delta H = -0.06659$ h

$H\text{-}C\equiv C\text{-}H + 2\ H\text{-}CN \rightarrow NC\text{-}CH_2\text{-}CH_2\text{-}CN$ (18) [20]

$\Delta H = -0.11007$ h

The partial reduction of 1,2-dicyanoethane to 3-cyanopropanimine is calculated as marginally unfavourable.

$NC\text{-}CH_2\text{-}CH_2\text{-}CN + H_2 \rightarrow NC\text{-}CH_2\text{-}CH_2\text{-}CH=NH$ (19) [21]

$\Delta H = 0.00233$ h

This will be used as one of the initial reactants although the molecules, 3-cyano-2-propynimine or 3-cyano-2-propenimine would also be entirely suitable.
These are the reactants that will be used in the synthesis of the amino acids, glutamine and glutamic acid.
The total energies and zero point energies for the HF and MP2/6-31G* equilibrium geometries for some of these stable molecules are given in Table 2.

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

Molecule	MP2 hartree	ZPE (HF) hartree
1,2-dicyanoacetylene(16)	-261.08706	0.02948

1,2-dicyanoethene (trans)(17)	-262.30636	0.05397
1,2-dicyanoethane(18)	-263.50719	0.07940
3-cyanopropanimine(19)	-264.66164	0.10419
L-glutamic acid (non-zwiterion) (20)	-550.02511	0.16462
Mg. HN=CH-CH_2–CH_2-CN.porphin (21)	-1449.82117	0.39272
Mg.1,3-cyanopropanimin-1-yl.porphin.CO (22)	-1562.81211	0.40299
Mg.1,(2-cyanoethyl) aziridine-3-one-1-yl.porphin. (23)	-1562.81915	0.40300
2-amino-4-cyano butanoic acid (24)	-453.94127	0.14687
L-glutamine (25)	-530.18127	0.17835
CH_4	-40.33255	0.04777
HCN	-93.15894	0.01799
CO	-113.02122	0.00556
H_2O	-76.19685	0.02298
NH_3	-56.35421	0.03700
H_3^+	-1.29643	0.02210
H_2	-1.14414	0.01059

4.1 The overall stoichiometry for the formation of L-glutamic acid.

Although Mg.porphin is here taken as the catalyst for the reaction, the overall stoichiometry to form the amino acid, L-glutamic acid is as follows,

$$H\text{-}C{\equiv}C\text{-}H + 2HCN + CO + 3H_2O + H_2 \rightarrow C_5H_9NO_4 + NH_3$$
(20) [22]

Fig.3. glutamic acid (non-zwitterion)

$\Delta H = -0.19326$ h

The enthalpy change is negative indicating that this may be the energetically favourable route to the initial formation of the amino acid. The intermediates by which this stoichiometric reaction may have occurred are as follows:

4.2 The formation of Mg-1,3-cyano-propanimin-1-yl.porphin.

The 3-cyano-propanimine forms a weak charge transfer complex with the catlalyst, Mg.porphin,

Mg.porphin + HN=CH-CH_2–CH_2-CN → Mg. HN=CH-CH_2–CH_2-CN.porphin
(1) (19) (21) [23]

$\Delta H = -0.04068$ h

The formal charge on the adduct is 0.059

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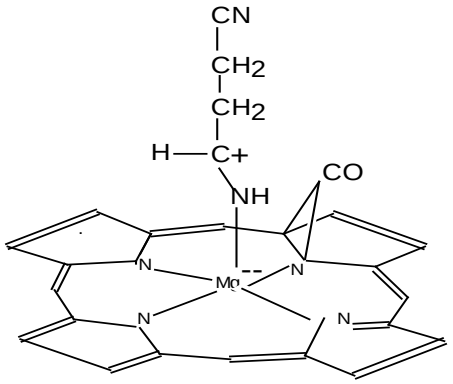
4.3 The formation of Mg.1,3-cyanopropanimin-1-yl.porphin.CO

For the correct formation of the L-isomer the 3-cyano propanimine needs to chelate to the magnesium ion on a Mg.porphin which has already obtained the correct orientation of a bound carbon monoxide molecule [13], as shown,

Mg.porphin.CO + 3-cyanopropanimine →
(6) (19)



Mg.1,3-cyanopropanimin-1-yl.porphin.CO (22) [24]

$\Delta H = -0.21757$ h

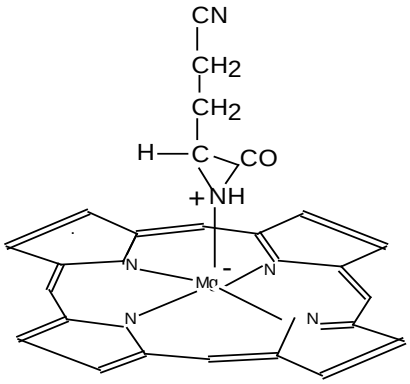
The enthalpy change is favourable and the activation energy to form van der Waals complexes is usually not significant if they are spontaneous.

4.4 The formation of Mg.1,(2-cyanoethyl) aziridine-3-one-1-yl.porphin.

The Mg.1,3-cyanopropanimin-1-yl.porphin.CO may easily rearrange to form Mg.1,(2-cyanoethyl) aziridine-3-one-1-yl.porphin with an activation energy of 0.149 h and a ring dissociation energy of 0.144 h. The enthalpy change is favourable.

$\Delta H = -0.00704$ h

The Mg.1,3-cyanopropanimin-1-yl.porphin.CO
(22) →



Mg.1,(2-cyanoethyl) aziridine-3-one-1-yl.porphin. (23) [25]

4.5 The formation L-glutamine and L-glutamate.

Hydrolysis in the reducing environment of the complex, is here depicted as releasing from the catalyst either the amide, glutamine, or with further hydrolysis.the undissociated glutamic acid, Fig.3. Further formation of the zwitterions may occur.

Mg.1,(2-cyanoethyl) aziridine-3-one-1-yl.porphin. + H_2O $\rightarrow$ Mg.porphin + L-2-amino-4-cyano-butanoic acid

(24) [26]

$$\Delta H = -0.03574 \text{ h}$$

Mg.1,(2-cyanoethyl) aziridine-3-one-1-yl.porphin. + **2**H_2O $\rightarrow$ Mg.porphin + L-glutamine

(25) [27]

$$\Delta H = -0.07132 \text{ h}$$

Mg.1,(2-cyanoethyl) aziridine-3-one-1-yl.porphin. + **3**H_2O $\rightarrow$ Mg.porphin + L-glutamic acid

[28]

$$\Delta H = -0.07228 \text{ h}$$

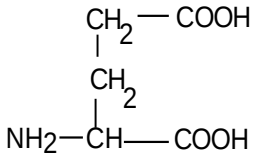


Fig.3 L-glutamic acid (non zwitterion) (20)

4. Conclusion

Direct reduction of simple volatile atmospheric cyanides to imines does provide a reasonable mechanism for the formation of all the amino acids considered.

For the formation of L-aspartic acid the 2-cyanoethan imine may have been formed in situ on the catalyst. Apart from the rate determining step involving the addition of ammonia to the alkyne, and ensuring a low rate of reaction, the remaining activation energies for the forward reactions have a lower, or comparable, value than the corresponding reverse reactions. Together with the achievable enthalpy changes these reactions do appear to be possible in a mildly reducing prebiotic atmosphere and should slowly produce some of these unique amino acids.. Further work at a higher accuracy may alter the values given here.

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