A Computational Study of a Prebiotic Synthesis of L-Threonine

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Abstract: - The magnesium ion metalloporphyrin complex is shown to bind the ligands propyne nitrile and propynimine in weak van der Waals complexes on the metal and nitrogen sites. Further reaction of the bound propynimine with carbon monoxide which 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, occurs to give a substituted aziridine-3-one that may easily cyclise to a bicyclic complex. Addition reactions involving hydrogenation followed by the addition of a molecule of water yield a 3-hydroxyethyl bicyclo complex that can be hydrolysed to the unique amino acid, L-threonine.
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-threonine, propyne nitrile, propynimine, Mg.porphin.

1 Introduction

The amino acid L-threonine (Thr,T), 2-Amino-3-hydroxybutanoic acid, is an essential amino acid [1], that occurs naturally as the L-isomer [2] and is present in many proteins such as insulin, myosin, and ovalbumin [3]. It has two asymmetric carbons such that it may exist in four different configurations. It shares this property with only one other common amino acid, L-isoleucine. The name L-threonine is used for one single isomer, (2S,3R)-2-amino-3-hydroxybutanoic acid. D-threonine is (2R,3S)-2-amino-3-hydroxybutanoic acid, whilst the two remaining stereoisomers are called L-allothreonine (2S,3S)-2-amino-3-hydroxybutanoic acid. and D-allothreonine (2R,3R)-2-amino-3-hydroxybutanoic acid, respectively [4].

L-threonine has a side-chain carboxyl pKa of 2.63, and an α-NH_2 pKa 10.43 [1,5]. The biosynthesis is from aspartate via the intermediate homoserine [1], or by the enzyme serine hydroxymethyltransferase catalyzing the reaction of acetaldehyde with glycine [1]. The oxidative degradation of threonine leads to acetaldehyde and glycine where the former is converted to acetyl-CoA [1]. The amino acid is involved in transcription by the codons ACT, ACC, ACA, and ACG [1].

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 [1,7] 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 in interstellar clouds [8-9], on Titan, a moon of Saturn [10], and as a major constituent (4%) in experiments on mixtures of gases of alkyne and nitrogen [11]. It has also been cited as a primary reactant in the prebiotic synthesis of the amino acids aspartic and asparagine, glutamic acid and L-glutamine [12] The presence of propynimine formed by the partial reduction of propyne nitrile, 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].

This paper proposes a model for the catalytic photochemically activated formation of L-threonine from the gases, propyne nitrile (cyanoacetylene) or from propynimine, carbon monoxide, water, 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 the predominant isomer, L-threonine 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 [15] commercial package. The standard calculations at the HF and MP2 levels including zero-point energy corrections at the Hartree Fock level, [16], together with scaling [17], 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 [16], 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 [15].
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)

Propyne nitrile has a negative formal charge on the alkyne methine carbon atom (-0.39) and a formal negative charge (-0.46) on the nitrogen atom of the cyanide group. It 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 [12] and an axial charge transfer complex. 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 (0.08), as follows,

Mg.porphin + NC-C ≡ C-H →
Mg.NC-C ≡ C-H.porphin
(1) (2) (3) [1]

$\Delta H =$ -0.02359 h

The enthalpy of formation of the van der Waals complex is small but it appears stable.
Although the enthalpy changes are comparable for the formation of in-plane [12] and axial complexes only the latter is used in this synthesis.

In a mildly reducing atmosphere the propyne nitrile may be expected to be partially reduced to propyne imine by free radical or ionic reactions, as

NC-C ≡ C-H + H_2 → HN = CH-C ≡ C-H
(2) (4) [2]

$\Delta H =$ -0.00021 h

This may also form a charge transfer complex with the catalyst Mg.porphin, as

HN=CH-C ≡ C-H + Mg.porphin →
Mg.1,HN=CH-C ≡ C-H.porphin
(5) [3]

$\Delta H =$ -0.03786 h

Both of these may be regarded as reactants in two similar reaction mechanisms where the initial reactant is either Mg.propynimine.porphin, described in detail here as first entry, followed by a subsection which pertains to the corresponding reaction from Mg.NC-C ≡ C-H.porphin by the second mechanism which leads to higher energy intermediates. These are tabulated in Table 1.

3.2 The Asymmetric Induction of Chirality

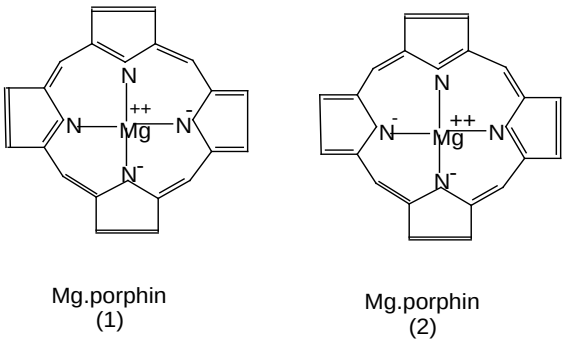
Mg.porphin also forms a stable complex [13] with carbon monoxide in which the carbon monoxide is bonded to the magnesium ion, as shown,

Mg.porphin + CO → Mg.CO.porphin
(1) (6) [4]

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

This is the low energy complex [13]. When this complex is photchemically activated, 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 [18] 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 [19]. In this model the molecule is described as a cyclic system [20] where the removal of the degeneracy of the orbitals by the

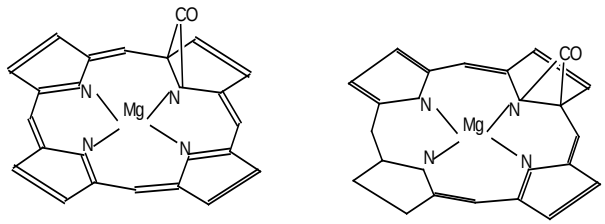
magnetic field allows the contributing mesomeric forms [21] to have different energies, as shown in Fig.1.



Mg.porphin (1) Mg.porphin (2)

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 [18] of which two are allowed by the selection rules [22]. As the molecule is normally diamagnetic [23] 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 [13,24-25] at a pyrrole unit with this isomer, as shown, Fig.2(1)



(1) (2)

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) (7)

$$\Delta H = 0.21136 \text{ h} \quad [5]$$

Mg.CO.porphin → Mg.porphin.CO
(6) (7) [6]

$$\Delta H = 0.20106 \text{ h}$$

These are the reactants that will be used in the synthesis of the amino acid, threonine.

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. (mechanisms 1&2)

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
propyne nitrile (2)	-169.07910	0.02989
Mg.NC-C ≡ C-H.porphin (3)	-1354.22108	0.31789
propynimine (4)	-170.23556	0.05408
Mg.1,propynimin-1-yl.porphin (5)	-1355.39257	0.34294
Mg.CO.porphin (6)	-1298.13452	0.29942
Mg.porphin.CO (7)	1297.93784	0.30434
L-threonine (non-zwitterion) (8)	-436.96368	0.15327
Mg.1,propynimin-N1-yl.porphin.CO (9)	-1468.34134	0.35281
Mg.1,propyne nitrilo-N1-yl.porphin.CO (10)	-1467.20683	0.32783
Mg.1,2-ethynyl-aziridin-3-one-N1-yl.porphin (11)	-1468.38912	0.35293
Mg.1,2-ethynyl azirin-3-one-N1-yl.porphin (12)	-1467.19455	0.32747
Mg.1,2-ethynyl-aziridin-3-one-N1dehydro-N1-yl.porphin^{-1} (13)	-1467.87216	0.33784
Mg.1,2-ethenyl aziridin-3-one-N1-dehydro-N1-yl.porphin (14)	-1468.28380	0.34815
Mg.1,bicyclo pent [2.1.0]-1-aza-2-en-5-oxo-N1-yl. porphin (15)	-1468.39021	0.35344

Mg.1,2-ethynyl aziridine-3-one-N1-dehydro-N1-yl.porphin $^+$ (16)	-1467.54854	0.34655
Mg.1,bicyclo [2.1.0] pent -1-aza-2-en-3-dehydro-5-oxo-N1-yl. porphin$^+$ (17)	-1467.43895	0.33544
Mg.1,bicyclo [2.1.0] pent -1-aza-3-hydroxy-5-oxo-N1-yl. porphin (18)	-1544.63086	0.38473
Mg.1,bicyclo [2.1.0] pent -1-aza-3-dehydro-5-oxo-N1-yl. porphin$^+$ (19)	-1468.72703	0.36418
Mg.1,2-(1-hydroxy ethyl) aziridin-3-one.porphin (20)	-1545.85069	0.40940
HCN	-93.15894	0.01601
CO	-113.02122	0.00556
H_2O	-76.19685	0.02298
NH_3	-56.35421	0.03700
OH-	-75.51314	0.00885
H_3^+	-1.29643	0.02210
H_2	-1.14414	0.01059

3.3 The Overall Stoichiometry for the Formation of L-threonine.

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

$$H\text{-}C \equiv C\text{-}CN + CO + 2H_2 + 2H_2O \rightarrow C_4H_9NO3 \quad (8) \quad [7]$$

Fig.2.threonine (non-zwitterion)

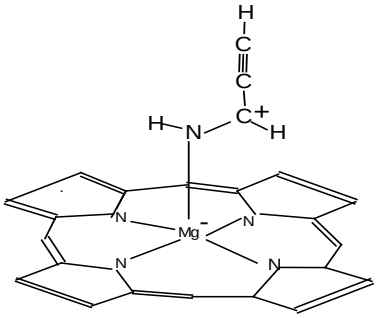
$\Delta H = -0.13627$ h

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, propynimin-N1-yl. porphin.

The propynimine may react with the catalyst, Mg.porphin, to form a weak charge transfer complex, as shown,

$$HN = CH\text{-}C \equiv C\text{-}H + \text{Mg.porphin} \rightarrow \text{Mg.1,}HN = CH\text{-}C \equiv C\text{-H.porphin} \quad (4) \quad [8]$$



Mg.1,propynimin-N1-yl.porphin. (5)

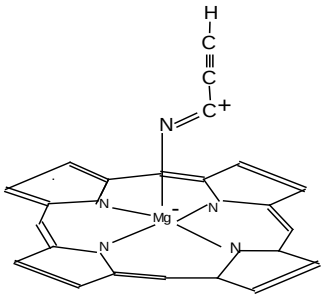
$\Delta H = -0.03786$ h

The enthalpy change is favourable and this weak complex forms without an activation energy. The adduct carries a charge of 0.05.

3.4.1 The Formation of Mg.1, propyne nitrilo -N1-yl. porphin.

Propyne nitrile may also react with the catalyst, Mg.porphin, to form a weak charge transfer complex, as shown,

$$N \equiv C\text{-}C \equiv C\text{-}H + \text{Mg.porphin} \rightarrow \text{Mg.1,}N = C\text{-}C \equiv C\text{-H.porphin} \quad (3) \quad [9]$$



Mg.1,propyne nitrilo-N1-yl. porphin. (3)

$\Delta H = -0.02359$ h

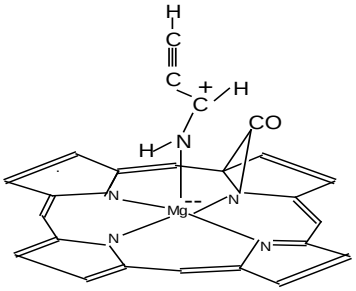
The enthalpy change is favourable and this weak complex forms without an activation energy. The adduct carries a charge of 0.03.

3.5 The Formation of Mg.1, propynimin-1-yl. porphin.CO

The propynimine may also form a charge transfer complex with the catalyst when it is already coordinated with a carbon monoxide molecule in the orientation dictated by the magnetic field of the exciting radiation and in an excited state, as shown,

propynimine + Mg.porphin.CO →

(4) (7)



Mg.1,propynimin-1-yl.porphin.CO (9) [10]

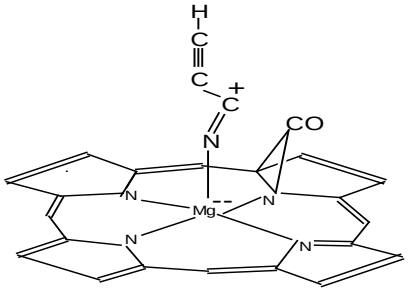
$\Delta H = -0.17294$ h

The enthalpy change is favorable. The adduct carries a charge of 0.17.

3.5.1 The Formation of Mg.1, propyne nitrilo-N1-yl. porphin.CO

The propyne nitrile may also form a charge transfer complex with the catalyst when it is already coordinated with a carbon monoxide molecule in the orientation dictated by the magnetic field of the exciting radiation and in an excited state, as shown,

Propyne nitrile + Mg.porphin.CO →
(2) (7)



Mg.1,propyne nitrilo-N1-yl. porphin.CO (10) [11]

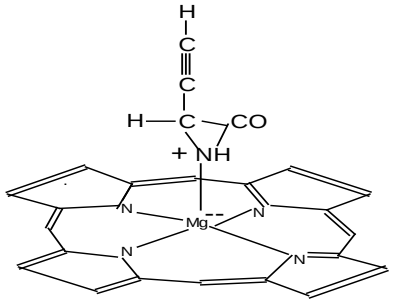
$\Delta H = -0.19558$ h

The enthalpy change is favorable. The adduct carries a charge of -0.07.

3.6 The Formation of Mg.1, 2-ethynyl aziridin-3-one-N1-yl.porphin

With only moderate activation energy the propynimine and carbon monoxide adducts may combine to form an aziridine complex, as shown,

Mg.1,propynimin-1-yl. porphin.CO →
(9)



Mg.1,2-ethynyl aziridin-3-one-N1-yl.porphin
(11) [12]

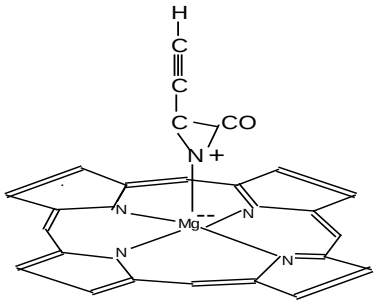
$\Delta H = -0.04766$ h

The activation energy to close the ring was calculated as 0.132 h, whilst that to open it was 0.133 h. The adduct carries a charge of 0.01. These values are comparable to those previously found for the formation of the amino acids [12].

3.6.1 The Formation of Mg.1, 2-ethynyl azirin-3-one-N1-yl.porphin

With only moderate activation energy the propyne nitrile and carbon monoxide adducts may combine to form an azirine complex, as shown,

Mg.1,propyne nitrilo-N1-yl.porphin.CO →
(10)



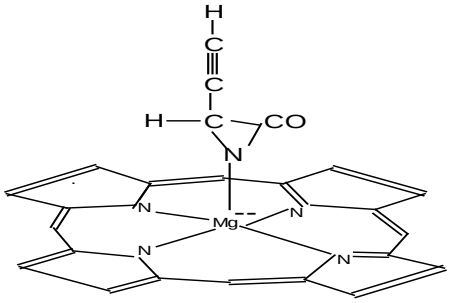
Mg.1,2-ethynyl azirin-3-one-N1-yl.porphin
(12) [13]

$\Delta H = 0.01196$ h

3.7 The Formation of Mg.1, bicyclo [2.1.0] pent-1-aza-2-en-5-oxo-N1-yl.porphin

The Mg.1,2-ethynyl-aziridin-3-one-N1-yl.porphin
may cyclise by reaction with the ethyne group by way of a transfer reaction, or by acid base catalysis to form a stable bicyclic adduct, as shown,

Mg.1,2-ethynyl aziridin-3-one-N1-yl.porphin + OH^- → H_2O +

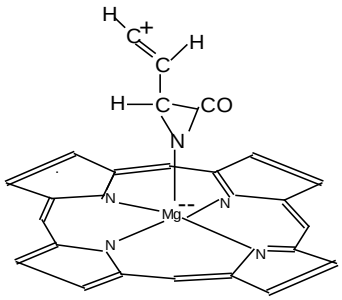


Mg.1,2-ethynyl aziridin-3-one-N1dehydro-N1-yl.porphin^{-1} (13) [14]

$$\Delta H = -0.16762 \text{ h}$$

The adduct carries a charge of -0.80.
If protonation occurs on the negatively charged adduct at C3 the adduct then carries a formal charge of -0.59. Protonation at C4 leads to some instability.

Mg.1,2-ethynyl aziridin-3-one-N1dehydro-N1-yl.porphin^{-1} + H^+ →

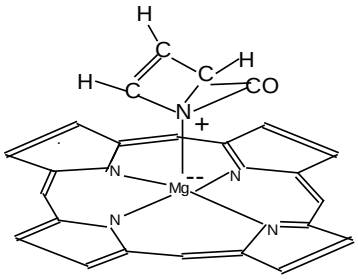


Mg.1,2-ethenyl aziridin-3-one-N1-dehydro-N1-yl.porphin (14) [15]

$$\Delta H = -0.40245 \text{ h}$$

The charges on C3 and C4 of the adduct are both -0.19.
The ring may then be cyclised with an activation energy of 0.11 h, where the activation energy to open the ring is also calculated as 0.11 h.

Mg.1,2-ethynyl-aziridin-3-one-N1-yl.porphin → (11)



Mg.1, bicyclo [2.1.0] pent -1-aza-2-en-5-oxo-N1-yl.porphin (15) [16]

$$\Delta H = -0.00065 \text{ h}$$

The enthalpy change is favourable.
However, the enthalpy change from the reaction,

Mg.1,2-ethenyl aziridine-3-one-N1-dehydro-N1-yl.porphin (14) →

Mg.1, bicyclo [2.1.0] pent -1-aza-2-en-5-oxo-N1-yl-porphin (15) [17]

is more favourable,

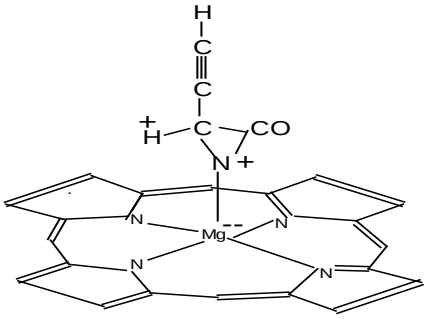
$$\Delta H = -0.10171 \text{ h}$$

The formation of this cyclic structure ensures that any addition of water must occur from above the surface of the complex, thus determining the C-3 configuration of the adduct uniquely.

3.7.1 The Formation of Mg.1, 2-ethynyl aziridin-3-one-N1-dehydro-N1-yl.porphin $^+$

The Mg.1,2-ethynyl azirin-3-one-N1-yl.porphin may react with a proton in a favourable reaction and then cyclise by reaction with the ethyne group.

Mg.1,2-ethynyl azirin-3-one-N1-yl.porphin + H^+ →



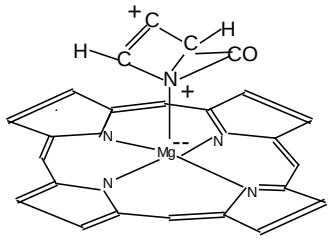
Mg.1,2-ethynyl aziridin-3-one-N1-dehydro-N1-yl.porphin $^+$ (16) [18]

$$\Delta H = -0.33701 \text{ h}$$

3.7.2 The Formation of Mg.1, bicyclo [2.1.0] pent -1-aza-2-en-3-dehydro-5-oxo-N1-yl. porphin

The Mg.1,2-ethynyl aziridin-3-one-N1-dehydro-N1-yl.porphin $^{+}$ may then cyclise, as shown,

Mg.1,2-ethynyl aziridin-3-one-N1-dehydro-N1-yl.porphin $^{+}$ →



Mg.1, bicyclo [2.1.0] pent-1-aza-2-en-3-dehydro-5-oxo-N1-yl.porphin^{+} (17) [19]

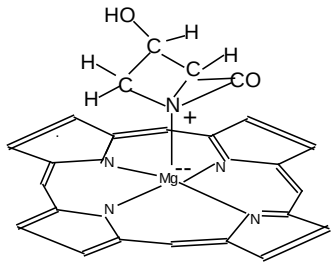
$$\Delta H = 0.09970 \text{ h}$$

The enthalpy change requires photochemical activation.

3.8 The Formation of Mg.1, bicyclo [2.1.0] pent -1-aza-3-hydroxy-5-oxo-N1-yl.porphin

The addition of a water molecule across the ethene double bond of Mg.1, bicyclo [2.1.0] pent -1-aza-2-en-3-dehydro-5-oxo-N1-yl. porphin could occur by free radical hydrogen and hydroxyl radicals in this environment or by hydrogen and hydroxyl ions, as shown,

Mg.1, bicyclo [2.1.0] pent-1-aza-2-en-3-dehydro-5-oxo-N1-yl.porphin + H_2O →



Mg.1,bicyclo [2.1.0] pent -1-aza-3-hydroxy-5-oxo-N1-yl.porphin (18) [20]

The enthalpy change is favourable.

$$\Delta H = -0.03640 \text{ h}$$

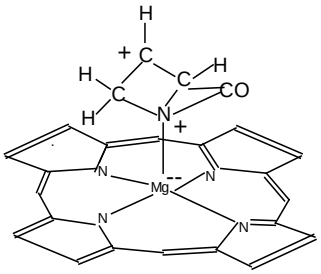
The addition of hydroxyl anion to the protonated adduct did not require any activation energy.

The entirely similar synthesis mechanism starting from the Mg.propyne nitrile.porphin complex and protonated on C1 is more specific in placing the hydroxyl group on C3 if the reaction is deemed ionic. If the hydroxyl anion is placed to give Mg.1, bicyclo pent [2.1.0]-1-aza-2-hydroxy-5-oxo-N1-yl. porphin then the synthesis would ultimately lead to the amino acid homoserine.

3.8.1 The Formation of Mg.1, bicyclo [2.1.0] pent -1-aza-3-dehydro-5-oxo-N1-yl. porphin^{+}

The further addition of a hydrogen molecule, followed by hydroxyl anion then produces the same product as the first mechanism from propynimine.

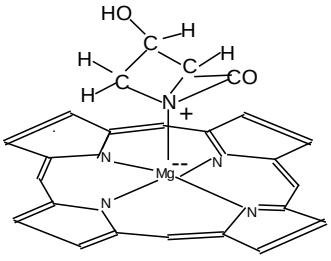
Mg.1, bicyclo [2.1.0] pent-1-aza-2-en-3-dehydro-5-oxo-N1-yl.porphin^{+} + H_2 →



Mg.1,bicyclo [2.1.0] pent -1-aza-3-dehydro-5-oxo-N1-yl.porphin^{+} (19) [21]

$$\Delta H = -0.12778 \text{ h}$$

Mg.1, bicyclo [2.1.0] pent-1-aza-3-dehydro-5-oxo-N1-yl.porphin^{+} + OH^{-1} →



Mg.1,bicyclo [2.1.0] pent-1-aza-3-hydroxy-5-oxo-N1-yl.porphin (18) [22]

The enthalpy change is favourable.

$$\Delta H = -0.38028 \text{ h}$$

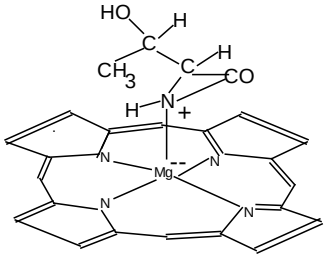
The addition of hydroxyl anion to the protonated adduct did not require any activation energy.
This synthesis is apparently more specific in placing the hydroxyl group on C3 if the reaction is deemed ionic This azetidine structure is found in some plant

amino acids where it may account for 50 % of the nitrogen present in the rhizome [26].

3.9 The Formation of Mg.1,2-(1-hydroxy ethyl) aziridin-3-one-N1-yl.porphin

Hydrogenation of the Mg.1,bicyclo [2.1.0] pent-1-aza-3-hydroxy-5-oxo-N1-yl. porphin is expected to be feasible in the mildly reducing atmosphere assumed, as shown,

Mg.1,bicyclo [2.1.0] pent -1-aza-3-hydroxy-5-oxo-N1-yl.porphin + H_2 →



Mg.1,2-(1-hydroxy ethyl) aziridin-3-one-N1-yl.porphin. (20) [23]

$$\Delta H = -0.06316 \text{ h}$$

The hydrogenation is here depicted for illustration purposes as homolysis of a hydrogen molecule occurring during the stretching of the C-C bond. The activation energy to sever the C-C bond was calculated at the HF level of accuracy as 0.151 h whilst that to restore it was 0.236 h.

3.10 The formation of L-threonine.

The hydrolysis of the Mg.1,2-(1-hydroxy ethyl) aziridne-3-one-N1-yl.porphin in a mildly alkaline environment is here depicted as releasing the catalyst and L-threonine, Fig.2. Further formation of the zwitterion may occur.

Mg.1,2-(1-hydroxy ethyl) aziridne-3-one-N1-yl. porphin + H_2O → Mg.porphin + L-threonine (8) [24]

$$\Delta H = -0.02661 \text{ h}$$

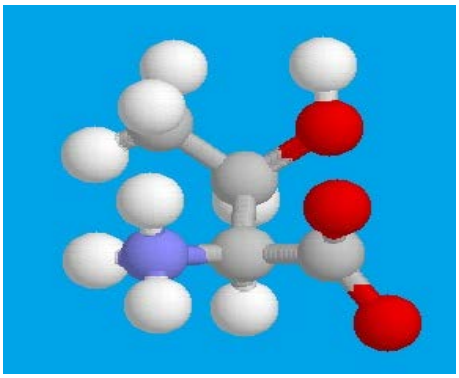


Fig.2: L-threonine (zwitterion) (8)

4 Conclusion

A previous postulated synthesis of (2S,3R)-L-threonine sought to determine the configuration of C2 of threonine where the initial reactant was propyne [27]. However, the configuration of C3 was left indeterminate, possibly giving rise to some of the (2R, 3S)-D-threonine. This synthesis from propyne nitrile should be more specific in determining the absolute configuration of (2S,3R)-L-threonine As both reaction mechanisms appear feasible it seems certain that there was a mixture of stereoisomers produced with a probable predominance of (2S,3R)-L-threonine

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

Acknowledgements:

Appreciation is expressed for the advice and support given to this project by Professor Curt Wentrup of the University of Queensland.

Appreciation is also expressed to APAC for facilities at the ANU and QMAS facilities at UQ, and the assistance of Mr.D.Green, H.Hartig, M.Hankel and M.Nicholls.

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