

A Computational Study of a Prebiotic Synthesis of L-Isoleucine

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Abstract— The magnesium ion metalloporphyrin complex is shown to bind the ligands pentdiyne nitrile and pentdynamine in weak van der Waals complexes on the metal site. 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, photochemical excitation may enable both adducts to combine to give a substituted aziridine-3one. Further photochemical excitation allows the formation of bicyclic and tricyclic adducts. Hydrogenation of this complex allows the opening of the rings to give an aziridine-3one that may easily hydrolyse to the zwitterionic form of L-isoleucine with the correct configuration.

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.

Keywords— L-isoleucine, prebiotic photochemical synthesis.

I. INTRODUCTION

THE The amino acid L-isoleucine (Ile,I), is an essential amino acid [1], that occurs naturally as the L-isomer [2] and is present in many proteins such as haemoglobin, elastin, wool keratin, myosin and ovalbumin [2]. Isoleucine contains two asymmetric carbon atoms and therefore exists in two racemic forms, DL-isoleucine and DL-alloisoleucine giving four optical isomers. The configuration of normal L-isoleucine is (2S, 3S)-2-amino-3-methyl pentanoic acid [1]-[3]. It has been shown to isomerise to D-alloisoleucine [4]. For isoleucine the α -COOH pKa is 2.4 and a α -NH₂ pKa 9.7 [5]. The biosynthesis of isoleucine is from α -ketobutyric acid followed by transamination [1]. The metabolism of isoleucine leads to succinyl-CoA [1]. (2S,3R,4S)-4-hydroxyisoleucine is found in the medicinal herb Fenugreek (*Trigonella foenum-graecum*) [6].

From a prebiotic perspective [7] 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]-[8] implying the presence of concentrations of carbon monoxide, ammonia, water and hydrogen. It is also supposed

that pentdiyne nitrile, H-(C \equiv C)₂-CN, that has been found in interstellar space [9]-[10] and present on Titan, a moon of Saturn, was also present, possibly formed from the free radical mediated condensation of diacetylene and hydrogen cyanide or by ionic species [11]. It has also been demonstrated that porphyrin may act as a catalyst for the formation of sugars [12], polyenes [13], and amino acids [14]-[15]-[16].

This paper proposes a model for the catalytic photochemically activated formation of L-isoleucine from pentdynamine, carbon monoxide, water and hydrogen, and the catalyst magnesium porphyrin.

The reactions described have been deduced as kinetically and thermodynamically viable, but photochemical excitation is required.

II. PROBLEM FORMULATION

This proposed computational study of a plausible synthesis of L-isoleucine 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 [17] commercial package. The standard calculations at the HF and MP2 levels including zero-point energy corrections at the Hartree Fock level, [18], together with scaling [19], using the same basis set, 6-31G*. are as previously published [7]. 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 [18], 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 [17].

1h = 627.5095 kcal.mol⁻¹. 1h = 4.3597482 x 10⁻¹⁸ J
Charges are in units of the electronic charge.

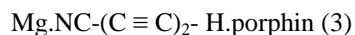
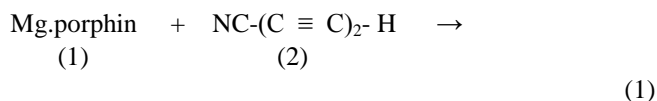
Appreciation is expressed to APAC for facilities at the ANU and QMAS facilities at UQ.

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III. PROBLEM SOLUTION

A. Total Energies (hartrees)

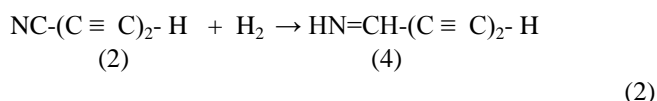
Pentdiyne nitrile may bond with the magnesium ion of magnesium porphin, which is here taken as a possible catalyst, to form a charge transfer complex where the charge on the ligand is positive, 0.08, and the charge on the porphin molecule is negative. The enthalpy of formation of the van der Waals complex is small but it appears stable.



$$\Delta H = -0.02674 \text{ h}$$

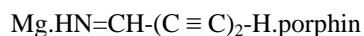
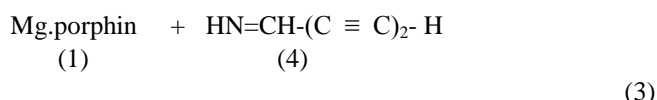
The adduct has formal charges of 0.30, -0.12, 0.37, 0.30, -0.60 on the carbons C1-C5, respectively.

In a mildly reducing atmosphere is also likely that the pentdiyne nitrile may be partially reduced to pentdiynimine, as



$$\Delta H = -0.00027 \text{ h}$$

This also forms a weak charge transfer complex with the catalyst Mg.porphin, as



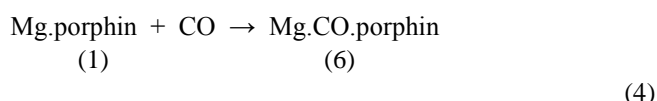
$$\Delta H = -0.04049 \text{ h}$$

Both of these can be regarded as primary reactants in two very similar mechanisms to form L-isoleucine. The first proceeds with higher energy intermediates as they are protonated on C1. The second mechanism is detailed here.

These are the first reactants required in the syntheses.

B. The asymmetric induction of chirality

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



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

This is the low energy complex [12]. When this complex is

photochemically activated, an in-plane electronic transition occurs in which the HOMO may be excited to the LUMO [12]. 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 [20] 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) [12]. The system of conjugated bonds in porphin has been approximated to the particle on a ring quantum mechanical problem [21]. In this model the molecule is described as a cyclic system [22] where the removal of the degeneracy of the orbitals by the magnetic field allows the contributing mesomeric forms [23] to have different energies, as shown in Fig.1.

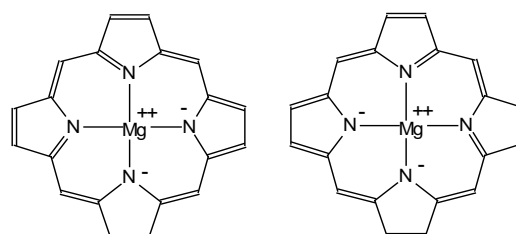


Fig.1. Mesomeric forms of Mg.porphin in the presence of a magnetic field pointing perpendicularly upwards from the ring towards the observer.

Four transitions may occur [20] of which two are allowed by the selection rules [24]. As the molecule is normally diamagnetic [25] the highest energy HOMO orbital should correspond to that shown as Fig.1 (left). 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-2-one ring [12]-[26]-[27] at a pyrrole unit with this isomer, as shown, Fig.2(1)

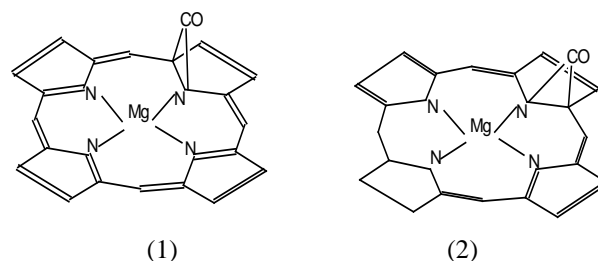
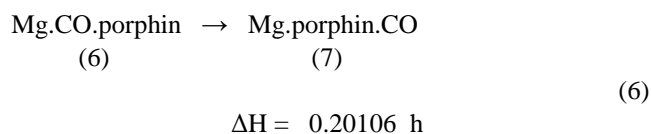
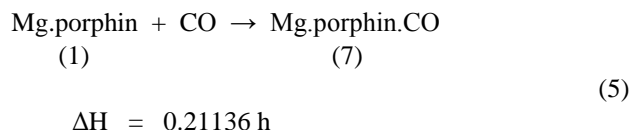


Fig.2. Isomers of Mg.porphin.CO

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 unfavourable 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 asymmetric 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.



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

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.

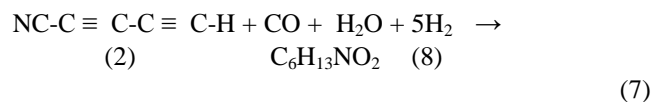
Table 1. MP2 /6-31G* total energies and zero point energies (hartrees) for the respective equilibrium geometries

Molecule	MP2 hartree	ZPE (HF) hartree
Mg.porphin (1)	-1185.12250	0.29262
pentdiyne nitrile (2)	-244.96962	0.04175
Mg.pentdiyne nitrilo.porphin (3)	1430.15104	0.32878
pentdiynimine (4)	-246.16311	0.06572
Mg.pentdiynimin-N-1yl.porphin (5)	-1431.32224	0.35400
Mg.CO.porphin (6)	-1298.13452	0.29942
Mg.porphin.CO (7)	-1297.93784	0.30434
L-isoleucine (non-zwitterion) (8)	-440.26559	0.20794
Mg.1, pentdiynimin-N1-yl.porphin.CO (9)	-1544.30392	0.36435
Mg.1,2-(butdiyn-1-yl) aziridin-3-one-N1-yl.porphin (10)	-1544.31703	0.36444
Mg.1,2-(butdiyn-1-yl) aziridin-3-one-N1dehydro-N1-yl.porphin ⁻¹ (11)	-1543.80515	0.34887
Mg.1,2-(buten-3-yn-1-yl) aziridin-3-one-N1dehydro-N1-yl.porphin (12)	-1544.30399	0.36948
Mg.1, bicyclo [2.1.0] pent-2-en-2-ethyn-5-oxo-N-1-yl.porphin (13)	-1544.31828	0.36398
Mg.1, tricyclo [4.1.0.0 ^{2,5}] hept-1-aza-2,3-dien-7-oxo -N1-yl.porphin (14)	-1544.21525	0.36382
Mg.1, tetracyclo [4.1.0.0 ^{2,5} .0 ^{2,4}] hept-1-aza-7-oxo -N-1-yl.porphin (15)	-1545.46982	0.39009
Mg.1, tricyclo [3.1.0.0 ^{2,4}] hex-1-aza-3-methyl-6-oxo-N1-yl.porphin (16)	-1546.71166	0.41473
Mg.1, bicyclo [2.1.0] pent-1-aza-3-ethyl-5-oxo-N-1-yl.porphin (17)	-1547.94205	0.44031

Mg.1,2-(1-methyl propyl) aziridin-3-one-N1-yl.porphin (18)	-1549.14474	0.46444
CO	-113.02122	0.00556
H ₂ O	-76.19685	0.02298
NH ₃	-56.35421	0.03700
OH ⁻¹	-75.51314	0.00885
H ₂	-1.14414	0.01059

C. The overall stoichiometry for the formation of L-isoleucine.

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



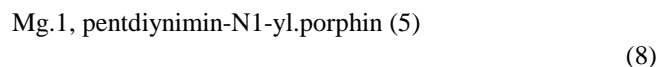
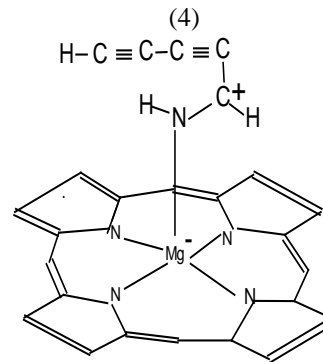
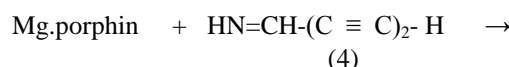
L-isoleucine(non-zwitterion)(8)

$$\Delta H = -0.24463 \text{ h}$$

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 these stoichiometric reactions may have occurred are as follows:

D. The formation of Mg.1, pentdiynimin-N1-yl.porphin.

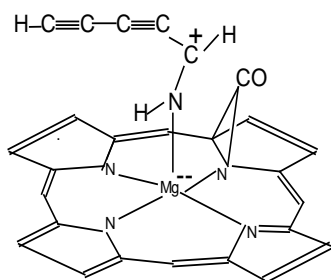
The pentdiynimine may form a weak charge transfer complex as,



$$\Delta H = -0.04049 \text{ h}$$

E. The formation of Mg.1, pentdiynimin-N1-yl.porphin.CO

The pentdiynimine may also form a weak charge transfer complex with Mg.porphin.CO where the carbon monoxide has been oriented by the magnetic field of exciting radiation, as



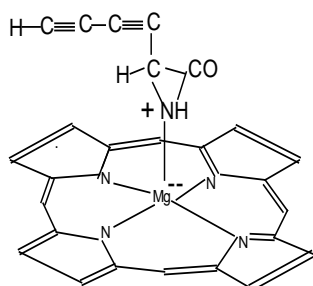
Mg.1,pentdiynimin-N1-yl.porphin.CO (9)

$$\Delta H = -0.20806 \text{ h}$$

The charge on the adducts is -0.04.

F. The formation of Mg.1, 2-(butdiyn-1-yl) aziridin-3one-N1-yl.porphin.

The Mg.1, pentdiynimin-N1-yl.porphin.CO may cyclise to form a more stable Mg.1, 2-(butdiyn-1-yl) aziridin-3one-N1-yl.porphin, as



Mg.1,2-(butdiyn-1-yl) aziridin-3one-N1-yl.porphin (10)

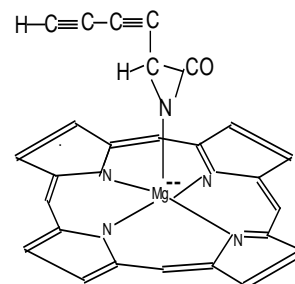
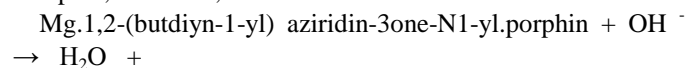
(10)

$$\Delta H = -0.01303 \text{ h}$$

The activation energy to form the aziridine- was found to be, 0.149 h, whilst the activation energy for the reverse reaction was 0.143 h.

G. The formation of Mg.1, bicyclo [2.1.0] pent-2-ethyn-5-oxo-N1-yl.porphin

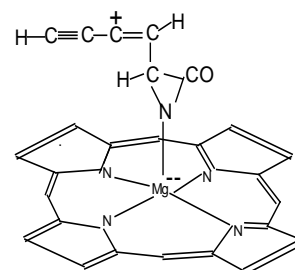
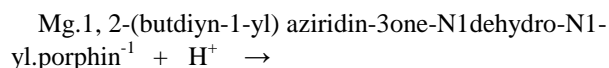
In a two step process the Mg.1,2-(butdiyn-1-yl) aziridin-3one-N1-yl.porphin may cyclise in which a proton is transferred followed by ring closure to give a bicyclic complex, as shown,

Mg.1,2-(butdiyn-1-yl) aziridin-3one-N1-dehydro-N1-yl.porphin⁻¹ (11)

(11)

$$\Delta H = -0.17310 \text{ h}$$

Protonation may then occur.



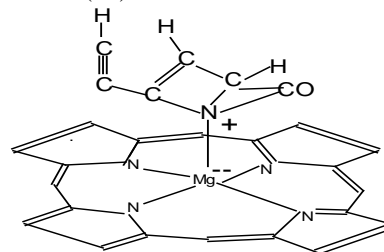
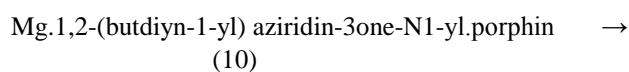
Mg.1,2-(buten-3-yn-1-yl) aziridin-3one-N1-dehydro-N1-yl.porphin (12)

(12)

$$\Delta H = -0.48049 \text{ h}$$

The ring may then be cyclised with an activation energy of 0.060 h, where the activation energy to open the ring is calculated as 0.069 h.

The net result is the following ring closure,



Mg.1,bicyclo [2.1.0] pent-1-aza-2-en-2-ethyn-5-oxo-N1-yl.porphin (13)

(13)

$$\Delta H = -0.00165 \text{ h}$$

The enthalpy change is favourable. The charge on the adduct was -0.39.

However, the enthalpy change from the reaction,

Mg.1, 2-(buten-3-yn-1-yl) aziridin-3-one-N1dehydro-N1-yl.porphin (12) \rightarrow

Mg.1, bicyclo [2.1.0] pent-1-aza-2-en-2-ethyn-5-oxo-N1-yl.porphin (13) (14)

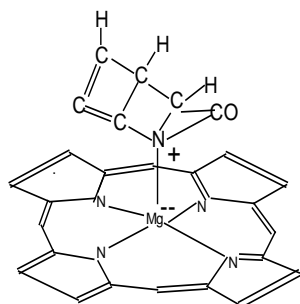
is more favourable,

$$\Delta H = -0.01919 \text{ h}$$

H. The formation of Mg.1, tricyclo [4.1.0.0^{2,5}] hept-1-aza-2,3-dien-7-oxo -N1-yl.porphin

It is postulated that the Mg.1, bicyclo [2.1.0] pent-1-aza-2-en-2-ethyn-5-oxo-N1-yl.porphin may further cyclise with photochemical excitation, as

Mg.1, bicyclo [2.1.0] pent-1-aza-2-en-2-ethyn-5-oxo-N1-yl.porphin \rightarrow



Mg.1, tricyclo [4.1.0.0^{2,5}] hept-1-aza-2,3-dien-7-oxo -N1-yl.porphin (14) (15)

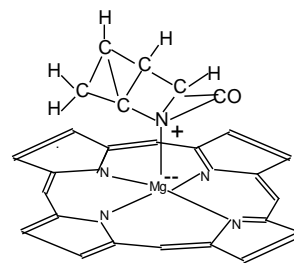
$$\Delta H = 0.10289 \text{ h}$$

The activation energy to close the ring was 0.117 h whilst that to open it was 0.017 h.

I. The formation of Mg.1, tetracyclo [4.1.0.0^{2,5}.0^{2,4}] hept-1-aza-7-oxo -N1-yl.porphin

Mg.1, tricyclo [4.1.0.0^{2,5}] hept-1-aza-2,3-dien-7-oxo -N1-yl.porphin (14) is formed as a high energy molecule and diradical which should be prone to hydrogenation. One step in the hydrogenation is postulated as shown,

Mg.1, tricyclo [4.1.0.0^{2,5}] hept-1-aza-2,3-dien-7-oxo -N1-yl.porphin (14) + H₂ \rightarrow



Mg.1, tetracyclo [4.1.0.0^{2,5}.0^{2,4}] hept-1-aza-7-oxo -N1-yl.porphin (15) (16)

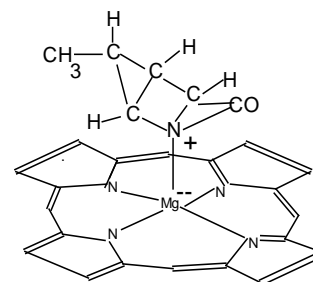
$$\Delta H = -0.09648 \text{ h}$$

The activation energy to hydrogenate by bringing a hydrogen molecule close to the diradical was 0.087 h, whilst the reverse activation energy was 0.197 h. The charge on the adduct was 0.01.

J. The formation of Mg.1, tricyclo [3.1.0.0^{2,4}] hex-1-aza-3-methyl-6-oxo-N1-yl.porphin (16)

Mg.1, tetracyclo [4.1.0.0^{2,5}.0^{2,4}] hept-1-aza-7-oxo -N1-yl.porphin (15) may be further hydrogenated in many ways where this sequence is designed to produce the desired end product.

Mg.1, tetracyclo [4.1.0.0^{2,5}.0^{2,4}] hept-1-aza-7-oxo -N1-yl.porphin + H₂ \rightarrow



Mg.1, tricyclo [3.1.0.0^{2,4}] hex-1-aza-3-methyl-6-oxo-N1-yl.porphin (16) (17)

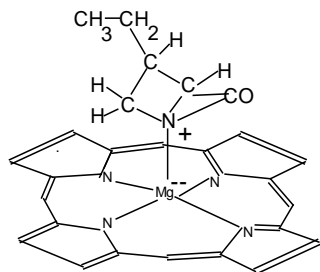
$$\Delta H = -0.08519 \text{ h}$$

The activation energy was found to be 0.194 h, whilst the activation energy for the reverse reaction was 0.312 h. The charge on the adduct was 0.02.

K. The formation of Mg.1, bicyclo [2.1.0] pent-1-aza-3-ethyl-5-N1-yl.porphin

Further hydrogenation of the Mg.1, tricyclo [3.1.0.0^{2,4}] hex-1-aza-3-methyl-6-oxo-N1-yl.porphin (16) should open the strained three membered cyclopropane ring, as shown,

Mg.1, tricyclo [3.1.0.0^{2,4}] hex-1-aza-3-methyl-6-oxo-N1-yl.porphin (16) + H₂ →



Mg.1, bicyclo [2.1.0] pent-1-aza-3-ethyl-5-oxo-N1-yl.porphin (17)

$$\Delta H = -0.07291 \text{ h}$$

(18)

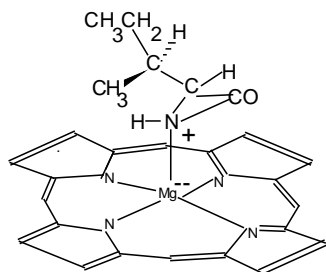
The activation energy for the hydrogenation was found to be 0.089 h, whilst the activation energy for the reverse reaction was 0.191 h. The charge on the adduct was 0.02.

If the three-membered ring was opened by hydroxyl anion this would lead to the naturally occurring (2S,3R,4S)-4-hydroxyisoleucine [6].

L. The formation of Mg.1, 2-(1-methyl propyl) aziridin-3-one-1-yl porphin.

A final hydrogenation at the quaternary nitrogen adduct should yield the desired aziridine adduct, as shown,

Mg.1, bicyclo [2.1.0] pent-1-aza-3-ethyl-5-oxo-N1-yl.porphin + H₂ →



Mg.1,2-(1-methyl propyl) aziridin-3-one-N1-yl.porphin (18)

$$\Delta H = -0.04649 \text{ h}$$

(19)

The activation energy for the hydrogenation was found to be 0.188 h, whilst the activation energy for the reverse reaction was 0.264 h.

M. The formation L-isoleucine.

Hydrolysis and hydrogenation in the reducing environment

of the complex, is here depicted as releasing from the catalyst the non-zwitterionic form of L-isoleucine. Further formation of the zwitterion may occur, Fig.3.

Mg.1,2-(1-methyl propyl) aziridin-3-one-1-yl.porphin + H₂O → Mg.porphin + L-isoleucine (8)

$$\Delta H = -0.03480 \text{ h}$$

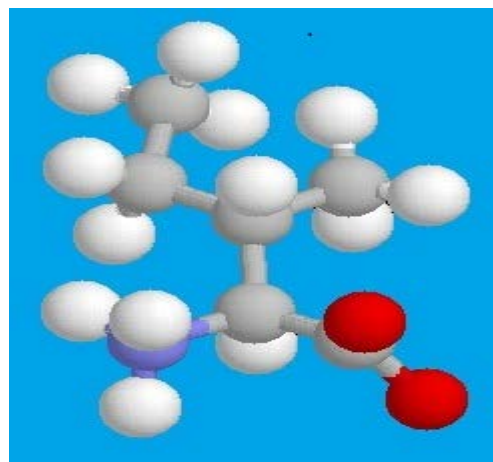


Fig.3. L-isoleucine (zwitterion) (8)

IV. CONCLUSION

This paper suggests that a simple interstellar molecule, butdiyne cyanide may have been an adduct in a surface catalysed photochemically activated reaction on the surface of the catalyst magnesium porphin containing a high energy pre-oriented carbon monoxide adduct to produce a complex where the magnetic field of the radiation induced the stereochemistry. The enthalpy changes and activation energies do appear attainable with this catalyst to produce over time some concentration of L-isoleucine.

A previous postulated synthesis from methyl diacetylene [28]. perhaps indicates that there is often more than one mechanism open to the formation of this unique molecule in the biosphere over a considerable period of time.

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

ACKNOWLEDGMENT

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Appreciation is also expressed for the assistance of Mr.D.Green, H.Hartig, M.Hankel and M.Nicholls

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