A Prebiotic Surface Catalysed Photochemically Activated Synthesis of α-Lipoic Acid

NIGEL AYLWARD
School of Chemistry and Molecular Biosciences
University of Queensland,
Brisbane, Queensland, Australia
uqnaylwa@uq.edu.au

Abstract: - Catalysts such as Mg.porphin may coordinate alkynes such as ethyne and catalyse their photchemically activated oligomerization. The multicentre catalyst may also form a charge transfer adduct with anions such as hydrogen disulphide anion centred on its magnesium ion. Both adducts may exhibit net negative charges which determine their orientations when subject to the magnetic field of exciting radiation. The preferred orientation determines the asymmetry of the adducts when they bond to form a complex. The negatively charged complex may then loose hydrogen anion to become neutral. Subsequent reaction with hydroxyl radicals to form a 1,1'-dihydroxy complex allows enolisation to form the carboxylic acid. Further hydrogenation and activation allows the separation of the α-lipoic acid from the catalyst.

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.

Key-Words: Ethyne, hydrogen disulphide, α-lipoic acid, Mg.porphin.

1 Introduction

Alpha-Lipoic acid, (R)-5-(1,2-Dithiolan-3-yl) pentanoic acid [1], pKa 5.10 [2], is a growth factor and a biocatalytic cofactor of the multienzyme complex pyruvic dehydrogenase [3] where it is obligatory for the entry of carbohydrates to the tricarboxylic acid cycle via pyruvate where they are oxidised to acetyl CoA and carbon dioxide [4]. In the tricarboxylic acid cycle it acts as a cofactor for the enzyme complex α-ketoglutaric dehydrogenase where α-ketoglutaric acid is oxidatively decarboxylated to succinyl-CoA and carbon dioxide [4]. It acts as a cyclic disulphide which readily undergoes reductive fission to a dithiol acid. It is a naturally occurring compound that is synthesized by both plants and animals. It is essential for aerobic life as we know it. It is biosynthesized by cleavage of linoleic acid [5]. Dithiolans may be synthesised from alkynes such as acetylene and sulphur [1]. α-lipoic acid may be synthesised by the oxidation of 6:8-dimercaptooctanoic acid [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 [3,8] implying the presence of concentrations of carbon monoxide, ammonia, water, hydrogen and hydrogen sulfide. It is also supposed that alkynes such as acetylene [9-10] were present as found on Titan, a moon of Saturn [11]. It has also been demonstrated that porphin may act as a catalyst for the formation of sugars [12] and polyenes [13].

This paper proposes a model for the catalytic photochemically activated formation of α-lipoic acid from the gas acetylene and hydrogen disulfide anion, water and the catalyst magnesium porphin. An experimental gaseous mixture subjected to discharge has also produced biomolecules [14].

2 Problem Formulation

The computations tabulated in this paper used the GAUSSIAN98 [15] commercial package. The standard calculations at the HF and MP2 levels including zero-point energy corrections [16], together with scaling [17], using the same basis set, 6-31G*. are as previously published [7]. All zero point energies are calculated as HF. 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].

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

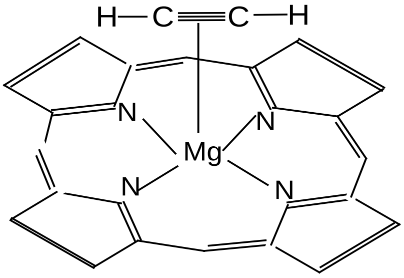
3 Problem Solution

3.1 Total Energies (hartrees)

The initial reactants are here taken to be acetylene, as this is known to form polyacetylenes in plants [18], hydrogen disulfide anion, and the photochemical catalyst Mg.porphin.

Mg.porphin is a powerful catalyst able to form charge transfer complexes with a number of different kinds of molecules [19]. With acetylene the ligand is positively charged (0.08) and the porphin has a negative charge [20]. The acetylene sets as ligand with a linear H-C ≡ C-H structure as shown.

Mg.porphin + H-C ≡ C-H → Mg.1,ethynyl .porphin
(1) (2) [1]



Mg.1,ethynyl .porphin (2)

Δ H = -0.01421 h

Sulfur occurs to the extent of 0.052 % in the Earth's crust [21] and often occurs in the elemental form at volcanoes. The source of the disulfide anion is here taken to arise from the reaction of elemental sulfur with alkaline sulfide solution [21], as,

$$S + S^{--} \rightarrow S\text{-}S^{--} \quad [2]$$

Δ H = -0.26040 h

The reaction appears to be energetic and polysulfides are known [21]. Further reaction of the disulfide anion gives the hydrogen disulfide anion,

$$H^{+} + S\text{-}S^{--} \rightarrow H\text{-}S\text{-}S^{--} \quad [3]$$

Δ H = -0.76670 h

The total energies and zero point energies for the HF and MP2/6-31G* equilibrium geometries for this molecule and the others involved in the synthesis 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
Mg.1,ethynyl.porphin (2)	-1262.19985	0.31797
Mg.porphin.ethynyl (3)	-1262.18547	0.31701
Mg.1,ethynyl.porphin.ethynyl (4)	-1339.27847	0.34849
Mg.1,1-buten-3-yl.porphin (5)	-1339.22814	0.34439
Mg.porphin.1-buten-3-yl (6).	-1339.2009	0.35468
Mg.1,ethynyl.porphin.1-buten-3-yl (7)	-1416.28042	0.38576
Mg.1,1,3-hexadien-5-yl.porphin (8)	-1416.07252	0.38686
Mg.porphin.1,3-hexadien-5-yl (9)	-1416.29897	0.38905
Mg.1, ethynyl.porphin.1,3-hexadien-5-yl (10)	-1493.50772	0.41995
Mg.1, 1,3,5-octatrien-7-yl.porphin (11)	-1493.50488	0.42385
Mg.porphin. 1,3,5- octatrien-7-yl (12)	-1493.44043	0.42409
Mg.1,hydrodisulfido.porphin. 1,3,5-octatrien-7-yl$^-$ (13)	-2289.37637	0.43561
Mg.1, 6-disulfanyl.porphin. 1,3,7-octatrien-1-yl-N-8-yl$^-$ (14)	-2289.44938	0.44357
Mg.1,6-disulfanyl.porphin.1,3-octadien-1-yl-N-8-yl$^-$ (15)	-2290.60533	0.47619
Mg.1, 6-disulfanyl.porphin. 1,3-octadien-1yl-ide-8N-yl**:** (16**)**	-2289.92041	0.46654
Mg.1, 6-disulfanyl.porphin. 1,3-octadien-1,1'-dihydroxy-N8-yl (17)	-2441.28712	0.50396
Mg.1, 6-disulfanyl.porphin.3-octen-1-carboxy-N8-yl (18)	-2441.32121	0.50479
5-(1,2-Dithiolan-3-yl) 3-pentenoic acid (19)	-1256.30606	0.20727
5-(1,2-Dithiolan-3-yl) pentanoic acid**,** lipoic acid (20)	-1257.49710	0.23279
S	-397.48197	
S^{--}	-397.33440	
$S\text{-}S^{--}$	-795.07764	0.00099

SSH^-	-795.85203	0.00963
H_2	-1.14414	0.01034
$OH^·$	-75.52257	0.00911
OH^-	-75.51314	0.00885
H_2O	-76.19685	0.02298

3.2 The overall stoichiometry for the formation of α-lipoic acid.

In the synthesis proposed here, there are two separate sequences.

In the first, an ethyne oligomer is formed followed by reaction with the hydrogen disulfide anion. The overall reaction may be represented as,

$$4\ H\text{-}C \equiv C\text{-}H + H\text{-}S\text{-}S^- + 2OH^{\bullet} + H^+ + H_2 \rightarrow C_8H_{14}O_2S_2 \qquad [4]$$

α-lipoic acid

$\Delta H = -1.12047$ h

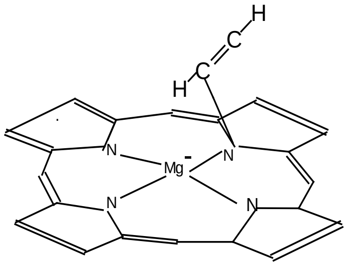
The enthalpy change is negative indicating that there may be energetically favourable routes to the prebiotic formation of this molecule.

3.3 The formation of ethyne oligomers on the surface catalyst, photochemically activated Mg.porphin.

3.3.1 The formation of Mg.porphin.ethynyl.

The Mg.ethynyl.porphin may be photochemically excited for the the ethyne to migrate to bond with a pyrrole unit as a higher energy ethyne adduct [13], as shown,

Mg.ethynyl.porphin →



Mg.porphin.ethynyl (3) [5]

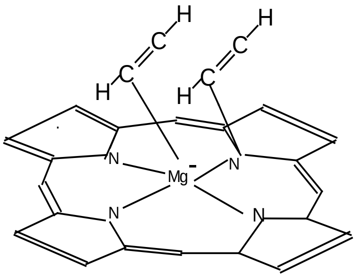
$\Delta H = 0.01353$ h

The activation energy is less than the first excitation energy of 0.21 h.

3.3.2 The formation of Mg.1, ethynyl. porphin. ethynyl.

The catalyst is then free to add another ethyne molecule, as shown,

Mg.porphin.ethynyl + H-C ≡ C-H →



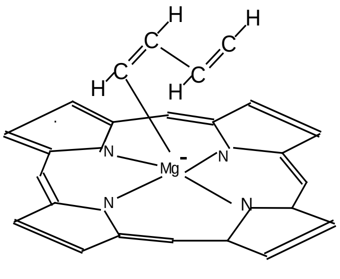
Mg.1, ethynyl.porphin.ethynyl (4) [6]

$\Delta H = -0.02440.$ h

3.3.3 The formation of Mg.1, 1-buten-3-yl.porphin

The Mg.ethynyl.porphin.ethynyl may be converted to Mg.1, 1-,buten-3yl.porphin as shown,

Mg.ethynyl.porphin.ethynyl →



Mg.1,1-buten-3-yl.porphin (5) [7]

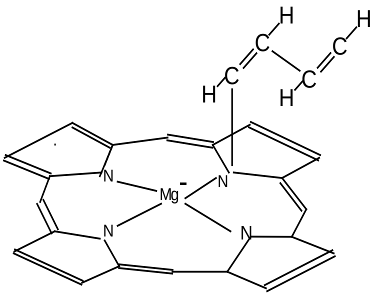
$\Delta H = 0.04668.$ h

The activation energy was calculated as 0.050 h, with no activation energy for the reverse reaction. The product is an unstable high energy compound.

3.3.4 The formation of Mg.porphin.1-buten-3-yl

In a similar manner Mg.1,1-buten-3-yl.porphin may be excited to a higher energy state where bonding is to the nitrogen atom of a neighboring pyrrole, as shown,

Mg.1,1-buten-3-yl.porphin →



Mg.porphin.1-buten-3-yl (6). [8]

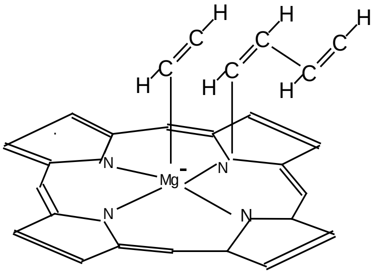
Δ H = 0.03636 h

The activation energy was found to be the enthalpy change..

3.3.5 The formation of Mg.1,ethynyl.porphin.1-buten-3-yl

Mg.porphin.1-buten-3-yl may bind another ethyne molecule in an energetically favourable reaction, as shown,

Mg.porphin.1-buten-3-yl + ethyne →



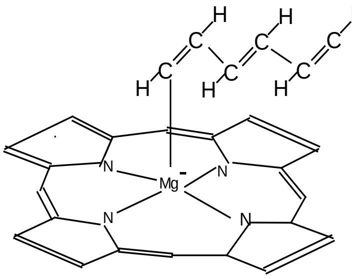
Mg.1,ethynyl.porphin.1-buten-3-yl (7) [9]

Δ H = -0.01124 h

3.3.6 The formation of Mg.1, 1,3-hexadien-5-yl.porphin.

Further activation enables the Mg.1,ethynyl.porphin. 1-buten-3-yl to form Mg.1,1,3-hexadien-5-yl.porphin, as shown,

Mg.1,ethynyl.porphin.1-buten-3-yl →



Mg.1, 1,3-hexadien-5-yl.porphin (8) [10]

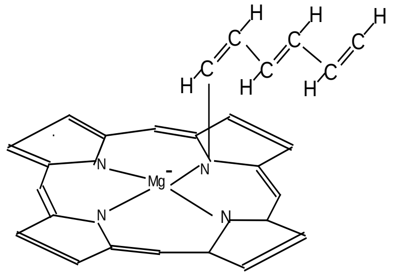
Δ H = -0.08098 h

The activation energy was calculated to be 0.208 h. It is a high energy compound.

3.3.7 The formation of Mg.porphin.1,3-hexadien-5-yl

The Mg.13-hexadien-5-yl.porphin may similarly be excited to form a higher energy adduct, as shown,

Mg.1, 1,3-hexadien-5-yl.porphin. →



Mg.porphin.1,3-hexadien-5-yl (9). [11]

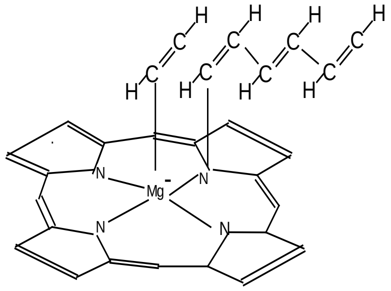
Δ H = 0.06537 h

The activation energy is the enthalpy change.

3.3.8 The formation of Mg.1,ethynyl.porphin. 1,3-hexadien-5-yl

The Mg.porphin.1,3-hexadien-5-yl may coordinate another ethyne molecule centered on the Mg^{++} ion of the Mg.porphin, as shown,

Mg.porphin.1,3-hexadien-5-yl →



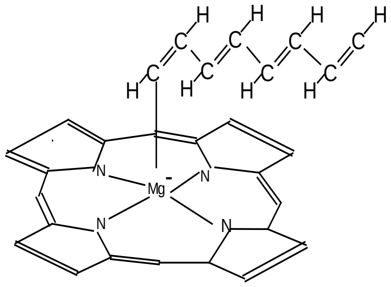
Mg.1,ethynyl.porphin.1,3-hexadien-5-yl (10) [12]

$\Delta H = -0.14067$ h

3.3.9 The formation of Mg.1, 1,3,5-octatrien-7-yl.porphin

The Mg.1,ethynyl.porphin.1,3-hexadien-5-yl may bond when activated to form Mg.1, 1,3,5-octatrien-7-yl.porphin, as shown.

Mg.1,ethynyl.porphin.1,3-hexadien-5-yl →



Mg.1, 1,3,5-octatrien-7-yl.porphin (11) [13]

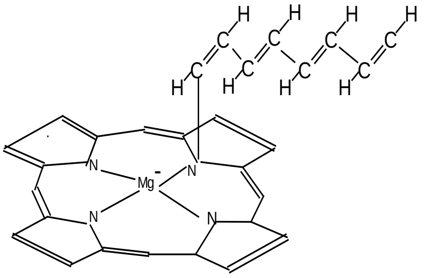
$\Delta H = 0.00712$ h

The activation energy was calculated as 0.004 h.

3.3.10 The formation of Mg.porphin. 1,3,5-octatrien-7-yl

With a last excitation the Mg.1, 1,3,5-octatrien-7-yl.porphin may form the final high energy product, as shown,

Mg.1, 1,3,5-octatrien-7-yl.porphin →



Mg.porphin. 1,3,5- octatrien-7-yl (12) [14]

$\Delta H = 0.06385$ h

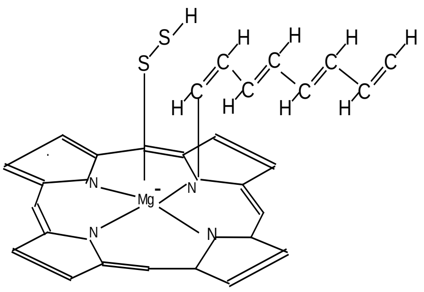
The activation energy is the enthalpy change.

The effect of this oligomerisation is that all coordinations of ethyne with the magnesium ion have a favourable enthalpy change, all promotions of the oligomer from the magnesium ion to a pyrrole nitrogen atom require enthalpy input. The entire sequence is favourable with a net enthalpy change of -0.03859 h. The reactions with a small positive enthalpy change are assumed to arise from the photochemical excitation of the Mg.porphin catalyst, 0.21 h. Without this electromagnetic excitation the reaction is not expected to produce significant product.

3.4 The formation of Mg.hydrodisulfido. porphin. 1,3,5-octatrien-7-yl

The Mg.octa-1,3,5-trien-7-yl.porphin may easily form a bond with the negatively charged hydrogen disulfide anion,

Mg.octa-1,3,5-trien-7-yl.porphin + SSH^- →



Mg.1,hydrodisulfido.porphin.1,3,5-octatrien-7-yl$^-$ (13) [15]

$\Delta H = -0.08221$ h

The negative charge is shared between the adducts so that the hydrosulfide has a charge of -0.180 and the tetraacetylene has a charge of -0.430 . When the molecule is excited both adducts are expected to rotate clockwise, when viewed from above the plane of the porphin, but they cannot pass [13]. There is however, a preferred orientation as shown in Fig.1. where the dihedral angle, Mg-N-C1-C2, has a value of -140 degrees, and the C1 and C2 refer to the closest carbons of the tetraacetylene adduct. This preferred orientation determines the stereospecificity of this molecule as the adducts bond.

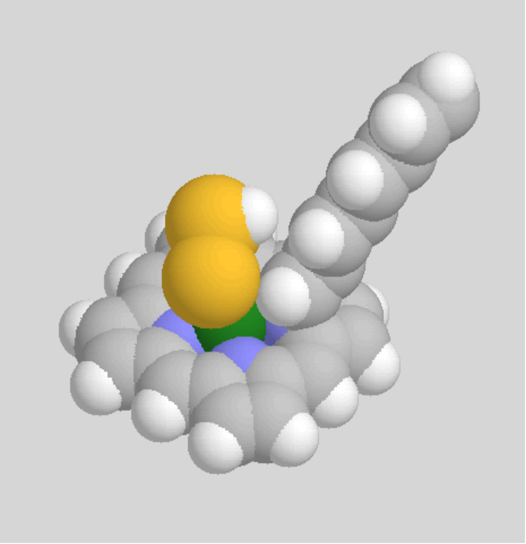
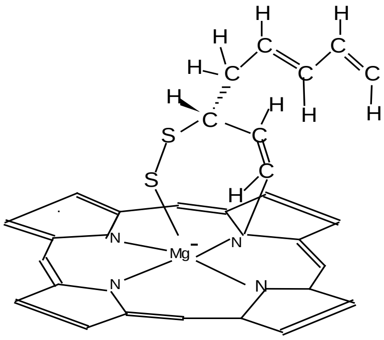


Fig.1. The preferred orientation of Mg.1,hydrodisulfido.porphin.1,3,5-octatrien-7-yl$^-$ with the adducts in a magnetic field perpendicular to the ring and pointing towards the observer.

3.5 The formation of Mg.1, 6-disulfanyl. porphin. 1,3,7-octatrien-1-yl-N-8-yl$^-$

The Mg.1, hydrodisulfido.porphin. 1,3,5-octatrien-7-yl$^-$ may bond to the tetra ethyne as shown,

Mg.1, hydrodisulfido.porphin. 1,3,5-octatrien-7-yl$^-$ →



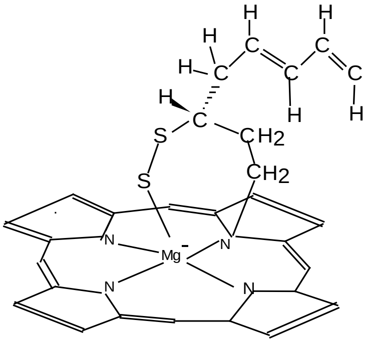
Mg.1,6-disulfanyl.porphin.1,3,7-octatrien-1-yl-N8-yl$^-$ (14) [16]

$$\Delta H = -0.06593 \text{ h}$$

The activation energy to close the ring by bringing the –SH group to the polyacetylene was 0.064 h.

3.6 The formation of Mg.1, 6-disulfanyl. porphin. 1,3-octadien-1-yl-N-8-yl

Mg.1, 6-disulfanyl.porphin. 1,3,7-octatrien-1-yl-N-8-yl$^-$ + H_2 .→

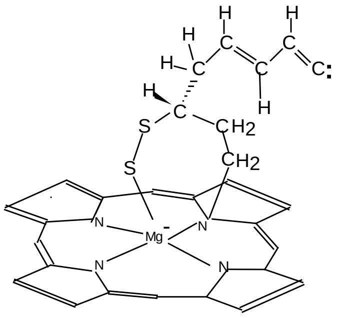


Mg.1, 6-disulfanyl.porphin.1,3-octadien-1-yl-N-8-yl$^-$ (15) [17]

$$\Delta H = -0.02446 \text{ h}$$

3.7 The formation of Mg.1, 6-disulfanyl. porphin. 1,3-octadien-1yl-ide-8N-yl:

Mg.1, 6-disulfanyl.porphin. 1,3-octadien-1-yl-N-8-yl$^-$ + H^+ → H_2 +

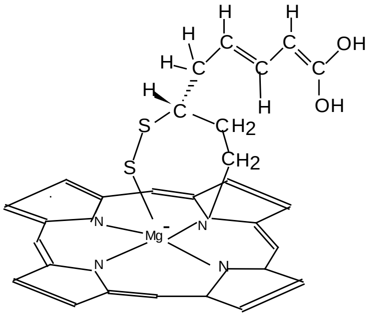


Mg.1, 6-disulfanyl.porphin.1,3-octadien-1yl-ide-8N-yl**:** (16) [18]

Δ H = -0.42935 h

3.8 The formation of Mg.1, 6-disulfanyl. porphin.1,3-octadien-1.1'-dihydroxy-N8-yl

Mg.1, 6-disulfanyl.porphin.1,3-octadien-1yl-ide-8N-yl**:** + 2OH$^{\bullet}$ →

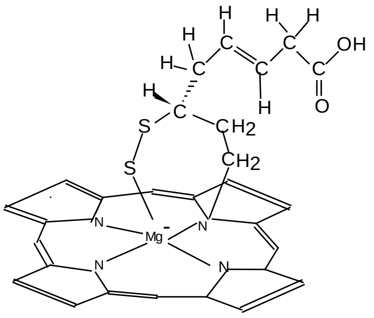


Mg.1, 6-disulfanyl.porphin. 1,3-octadien-1,1'-dihydroxy-N8-yl (17) [19]

Δ H = -0.30448 h

3.9 The formation of Mg.6-disulfanyl.porphin.3-octen-1-carboxy-N8-yl

Mg.1, 6-disulfanyl.porphin.1,3-octadien-1,1'-dihydroxy-N8-yl . →

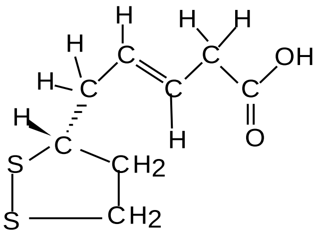


Mg.1, 6-disulfanyl.porphin.3-octen-1-carboxy-N8-yl (18) [20]

Δ H = -0.03335 h

3.10 The dissociation of Mg.1, 6-disulfanyl. porphin.3-octen-1-carboxy-N8-yl

Mg.6-disulfanyl.porphin.3-octen-1-carboxy-N8-yl → Mg.porphin +



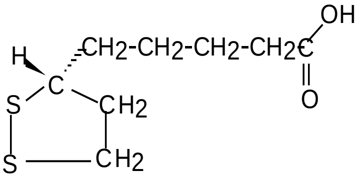
5-(1,2-Dithiolan-3-yl) -3-pentenoic acid (19) [21]

ΔH = -0.11171 h

Although energetically favourable this reaction requires the reactant to be in a higher energy activated state for the dissociation to occur. This was achieved by stretching the adduct C-N bond with an input of 0.038 h

3.11 The hydrogenation of 5-(1,2-Dithiolan-3-yl) -3-pentenoic acid

5-(1,2-Dithiolan-3-yl) -3-pentenoic acid + H_2 →



5-(1,2-Dithiolan-3-yl) pentanoic acid**,** Lipoic acid
(20) [22]

$$\Delta H = -0.03362 \text{ h}$$

4. Conclusion

These calculations provide a rational explanation according to the laws of chemical thermodynamics and kinetics for the existence and synthesis of this important molecule in a particular stereospecificity from reactants known to be abundant in the biosphere, provided the Earth's original atmosphere was mildly reducing with some hydrocarbon present.

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

5 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 the National Computing Infrastructure facility supported by the Australian Government (grant NCI-MAS g01) and QCIF, and the assistance of Mr.D.Green, H.Hartig and M.Hankel

References

[1] J.D.Loudon in E.H.Rodd (Ed.), *Chemistry of Carbon Compounds,*Vol.1VA, Elsevier Publ.Comp. 1957, pp.333.

[2] A.Volpi and F.Toffoli, Therapeutic dosage and physicochemical constants of bases and acids, *Boll. Chim. Farm.*, 118, 1979, pp.594-609.

[3] A.L.Lehninger, *Biochemistry,*Worth, New York ,1975.

[4] E.E.Conn and P.K.Stumpf, *Outlines of biochemistry*, Wiley Int.1972.

[5] J.D.Carreau, Biosynthesis of lipoic acid via unsaturated fatty acids, *Methods Enzymology*, 62, 1979, pp.152-8.

[6] L. J. Reed, I. C. Gunsalus, G. H. F. Schnakenberg, Q.F. Soper, H.E. Boaz, S. F. Kern, and T. V. Parke, *J. Am. Chem. Soc., 75* (6), 1953, pp. 1267–1270.

[7] N.Aylward, and N.R.Bofinger, Possible origin for porphin derivatives in prebiotic chemistry - a computational study, *Orig.Life Evol. Biosph.*,35, No.4, pp345-368,2005.

[8] S.L.Miller and L.E.Orgel, *The Origins of Life on Earth*, Prentice-Hall Inc.,Englewood Cliffs, N.J. ,1975.

[9] D.W.Clarke and J.P.Ferris, Photodissociation of cyanoacetylene : application to the atmospheric chemistry on Titan, *Icarus*, vol.115,1995, pp.119-125.

[10] K.Seki, M.He, R.Liu and H.Okabe, Photochemistry of cyanoacetylene at 193.3 nm., *J.Phys.Chem*.,100 ,1996, pp.5349-5353.

[11] Z.Guennoun, A.Coupeaud, I.Couturier-Tamburelli, N.Pietri, S.Coussan, J.P.Aycard, Acetylene/cyanoacetylene complexes:simulation of the Titan's atmosphere chemistry, *Chem.Phys*.300, 2004, pp.143-151.

[12] N.N.Aylward, and N.R.Bofinger, Carbon monoxide clusters in the formation of D-sugars and L-amino-acids in prebiotic molecular evolution on Earth, in G.Palyi, C.Zucchi, L.Cagliotti, eds., *Progress in Biological Chirality*, Elsevier,Oxford (GB), 2004, ch2, pp.429.

[13] N.N. Aylward, The synthesis of terpenes in prebiotic molecular evolution on Earth, in WSEAS *New Aspects of Biomedical Electronics and Biomedical Informatics*. Eds. C.A.Long, P.Anninos, T.Pham, G.Anastassopoulos, N.E.Mastorakis, 2008, pp.202-207

[14] E T. Parker, H. J. Cleaves, M. P. Callahan, J. P. Dworkin, D. P. Glavin, A. Lazcano, J. L. Bada, Prebiotic synthesis of methionine and other sulfur-containing organic compounds on the primitive Earth: A contemporary reassessment based on an unpublished 1958 Stanley Miller experiment, *OLEB*, 41, No.3, 2011, pp. 201–212.

[15] Gaussian98, *Users Reference,Gaussian* Inc.,Carnegie Office Park, Bldg.6., Pittsburgh, PA 15106, USA,1998.

[16] W.J.Hehre, L.Random, P.V.R. Schleyer, and J.A.Pople, *Ab Initio Molecular Orbital Theory,* Wiley, New York.,1986.

[17] J.A.Pople, H.B.Schlegel, R.Krishnan, D.J. DeFrees, J.S. Binkley, M.J. Frisch, R.A.Whiteside, R.J.Hout and W.J.Hehre, Molecular orbital studies of vibrational frequencies, *Int.J.Quantum Chem. Symp*. vol.S15,1981, pp.269-278.

[18] L.P.Christensen and K.Brandt, Bioactive polyacetylenes in food plants of the Apiacae family: occurrence, bioactivity and analysis, *J.Pharm. Biomed.Analysis,* 41, 2006, pp.683-693.

[19] D.G.Whitten,I.G.Lopp and P.D.Wildes, Fluorescence of zinc and magnesium etioporphyrin 1. quenching and wavelength shifts due to complex formation, *J.Am.Chem.Soc*., 90, 1968, pp.7196-

7200.
[20] N. Aylward, A prebiotic surface catalysed synthesis of alkyl imines,in WSEAS Int. Conf. on *Biomedical Electronics and Biomedical Informatics*. Moscow, Russia, August 20-22, 2009, pp.52-59.
[21] T.Moeller, *Inorganic Chemistry*, J.Wiley, 1952