A Computational Study of a Prebiotic Synthesis of a Tripeptide: Thyrotropic Releasing Hormone (TRH)

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Abstract: - Ab initio calculations are used to calculate the viability of a prebiotic mechanism for the synthesis of L-proteins considered as a one-dimensional cooperative system having interlocking terms involving two neighbouring amino-acid residues yielding the inter-bond energy, optimum conformation, and charge distribution leading to an estimate of the secondary structure. The prebiotic synthesis of poly amino acids is illustrated with the synthesis of a tripeptide, thyrotropic releasing hormone. The magnesium ion metalloporphyrin complex is shown to bind the prebiotic stereospecific ligand precursors of the amino acids proline, histidine, and pyroglutamic on the metal or nitrogen pyrrole sites as a two-site catalyst in their copolymerization to form Glu-His-Pro-NH_2. The order of addition of the monomers is the reverse of pyroglutamylhistidinylprolamide to form the tripeptide. which is separated from the catalyst by hydrogen ions. The reactions are 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 stereospecific poly amino acid synthesis, thyroid releasing hormone.

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1 Introduction

Computational chemistry has been used to determine an estimate of the secondary structure, [1] and tertiary structures of proteins, [2], [3], [4], from protein sequence, by comparative homology analysis, [5], and by incorporating machine learning into quantum mechanical calculations, [6]. The energy of a protein may be considered to have interlocking terms which depend on conformations of at least two neighboring amino acid residues and is a one-dimensional cooperative system, [7]. Abinitio calculations may be utilized to calculate the bonding energy and estimate the lowest energy conformation for each of the added amino acids, [8] to generate the entire sequence where each pair of interlocking amino acids has an optimum conformation leading to a predicted secondary structure. A prebiotic mechanism is invoked to show how stereospecific L- reactants could react to form an L-protein. The calculations are used to justify the mechanism with regard to enthalpy changes and activation energies. The protein chosen to test the mechanism and viability of the methodology is a small protein thyrotropin releasing hormone (TRH).

The tripeptide, thyrotrophin-releasing hormone, (TRH), is one of the simplest peptides, Glu-His-Pro-NH_2, [9], [10]. It is responsible for stimulating the release of thyrotrophin (thyroid-stimulating hormone, TSH) from the anterior pituitary gland, [11], [12]. The main function of TSH is to control the release of the thyroid hormones, thyroxine (T4) and tri-iodothyroxine (T3) from the thyroid gland. A feedback control of TSH secretion, either directly or by inhibiting TRH, is exerted by T3 and T4, [12], [13].

From a prebiotic perspective, [14], it is desirable if the reactant molecules, derivatives of aziridones formed spontaneously from a supposed prebiotic atmosphere often held to have been originally mildly reducing, [11], [15], implying the presence of concentrations of carbon monoxide, ammonia, water, and hydrogen. It has also been demonstrated that porphin present from the time of photosynthesis, [16], may act as a catalyst for the formation of D-sugars, L-amino acids, [17], and terpenes, [18].

This paper proposes a model for the catalytic photochemically activated copolymerization of substituted aziridone precurors of the amino-acids, prolamide, [19], histidine, [20], and pyroglutamic acid, [21], where the order of addition is the reverse of Glu-His-Pro-NH_2. Initiation of the polymerization occurs at C-terminal prolamide end

of the tripeptide, propagates through the histidine residue, and terminates at the N-terminal of the pyroglumate amino acid with separation of the metal porphin catalyst. Molecules that have strained structures such as aziridine, azetidine, iminoethylene derivatives, and aziridones are easily polymerized, [22], [23].

The synthesis of this biochemical tripeptide hormone is postulated to be an example of a general mechanism for the stereospecific prebiotic synthesis of any polypeptide, presumed to be of the order of 23^{100}, from the prebiotic era from stereospecific aziridone precursors formed over a considerable period of time.

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 tripeptide thyroid releasing hormone (TRH)l involves the calculation of the enthalpy changes for reaction intermediates in the ZKE approximation and the calculation of activation energies at the HF level. These activation energies may all be accessible as the catalyst may absorb appreciable photochemical activation, (0.21 h). The computations tabulated in this paper used the GAUSSIAN09, [24].

The standard calculations at the HF and MP2 levels including zero-point energy corrections at the Hartree Fock level, [25], together with scaling, [26], using the same basis set, 6-31G*. are as previously published, [14], and activation energies calculated at the HF level without scaling are less accurate. All amino acids, dipeptide, and tripeptide are of the L-configuration, [27].

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, [24].

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

Mulliken charges are in units of the electronic charge.

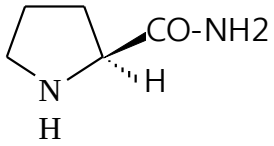
3 Problem Solution

3.1 Total Energies (Hartrees)

The formation of initial reactants is predicated on the stereospecific formation of the prebiotic aziridone precursors of the amino acids proline, [19], histidine, [20], and glutamic acid, [21]. However, some initial modification of these aziridones is required for the synthesis of this unique tripeptide.

For prolamide to be present, the corresponding aziridone, [19], or proline may react with ammonia according to the reaction,

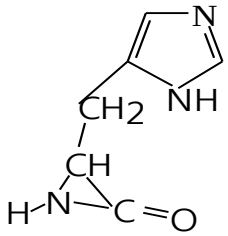
$C_5H_9NO_2 + NH_3 \rightarrow H_2O +$ proline (1)



prolamide, (2) $C_5H_{10}N_2O$

$\Delta H = 0.00496$ h

The histidine aziridone is unaltered from its prebiotic synthesis, [20].

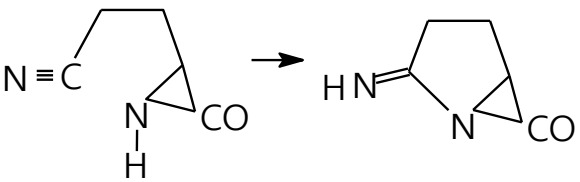


2-(4-iminazoyl methanyl) aziridin-3-one (3)

The final amino acid is pyroglutamic acid which is a rare amino acid. Glutamic acid and its amide reach an equilibrium in water, [28], to produce pyroglutamic acid, as shown,

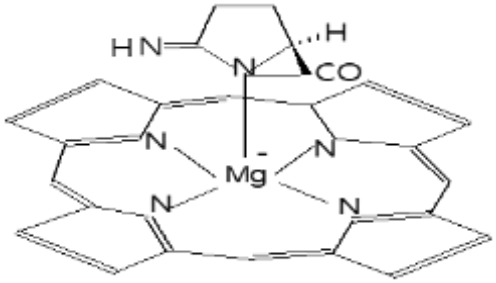
$C_5H_9NO_4 \rightarrow C_5H_7NO_3 + H_2O$
glutamic acid pyroglutamic acid

It is suggested that this rare amino acid was formed from a cyclic imidine in the prebiotic synthesis of the L-glutamic acid precursor as shown,



This may have occurred on the catalyst, Mg.porphin, for activation energy, as,

1,2-(2-cyanoethyl) aziridine-3-one-1-yl →
(4)

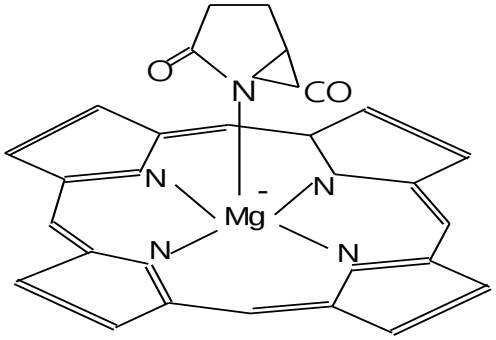


Mg.1,1-azabicyclo [5:1:0] 2-imido-6-keto hexan-N1-yl.porphin (5)

$\Delta H = 0.00722$ h

Hydrolysis of the imidine in aqueous solution yielding the pyroglutamyl reactant as

Mg.1,1-azabicyclo [5:1:0] 2-imido-6-keto hexan-N1-yl.porphin + $H_2O \rightarrow NH_3$ +

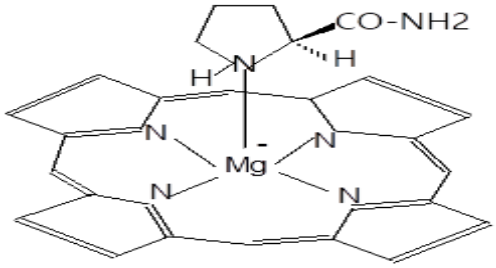


Mg.1,1-azabicyclo [5:1:0] 2,6-diketo hexan-N1-yl.porphin (6)

$\Delta H = -0.04983$ h

Each of these aziridones may form adducts with the catalyst on the metal and N-pyrrole sites. The enthalpy of formation of the van der Waals complex is small but it appears stable.
Mg.porphin is a powerful catalyst able to form charge transfer complexes with a number of different kinds of molecules, [29], [30].
With prolamide the ligand is positively charged (0.08) and the porphin has a negative charge, [19]. The Mg-N bond is formed as shown,

Mg.porphin + prolamide →

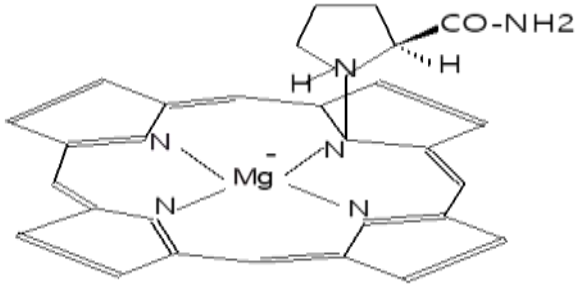


Mg.1,prolamid-N1-yl.porphin (7)

$\Delta H = -0.04567$ h

The charge on the prolamide adduct is -0.145
The Mg.1,prolamid-1-yl.porphin may be photochemically excited for the prolamide to migrate to bond with a pyrrole unit as a higher energy adduct, [19], as shown,

Mg.1,prolamid-1-yl.porphin → (7)

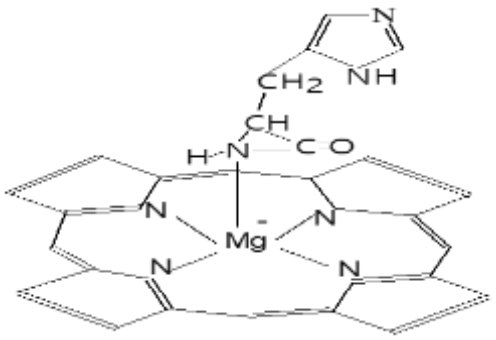


Mg.1, porphin.prolamid-N1-yl (8)

$\Delta H = 0.12154$ h
The charge on the adduct is -0.132.
For the above complex, where the adduct is $C_4H_8CONH_2$, the charge on the adduct ring nitrogen is -0.767, and that on the amide nitrogen is -0.926.
For the corresponding zwitterion form, $C_4H_7CONH_3$, the charge on the ring nitrogen is -0.768, and the amide nitrogen is -0.897.
The ring nitrogen is a plausible nucleophile and a high-energy molecule.

The 2-(4-iminazoyl methanyl) aziridin-3-one may also form two adducts with the catalyst on the metal and N-pyrrole sites, as follows:
The enthalpy of formation of the van der Waals complex is small but it appears stable.

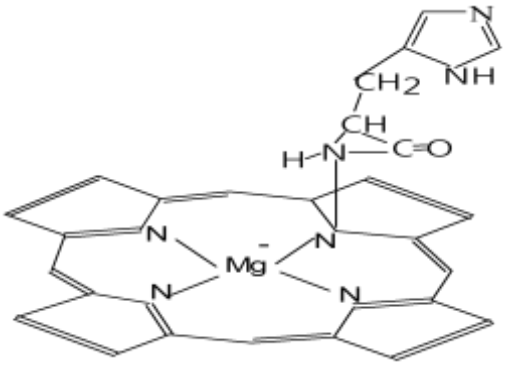
Mg.porphin + 2-(4-iminazoyl methanyl) aziridin-3-one →
(1) (3)



Mg.1,2-(4-iminazoyl methanyl) aziridin-3-one.porphin) (9)

ΔH = -0.04555 h
The charge on the adduct is 0.048.
A high-energy adduct may also be formed by photochemical excitation as,

Mg.1, 2-(4-iminazoyl methanyl) aziridin-3-one (9) →

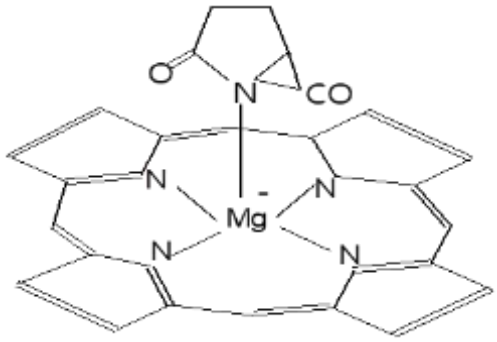


Mg.1,porphin.2-(4-iminazoyl methanyl) aziridin-3-one.porphin (10)

ΔH = 0.04596 h
The charge on the histidine adduct was -0.010.

The pyroglutamyl aziridone may also form stable adducts as,

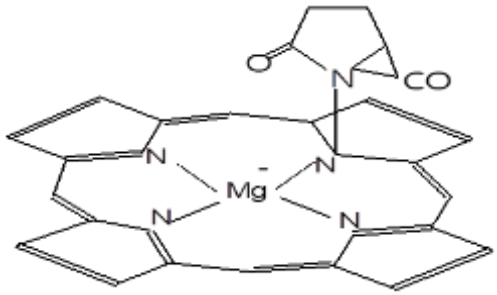
Mg.porphin + 1-azabicyclo [5:1:0] 2-6-diketo hexane →
(11)



Mg.1,1-azabicyclo [5:1:0] 2-6-diketo hexan-N1-yl.porphin (6)

ΔH = -0.04549 h
The charge on the pyroglutamyl adduct is -0.013.

The adduct may be excited to a stable excited state.
Mg.1,1-azabicyclo [5:1:0] 2-6-diketo hexan-N1-yl.porphin (6) →



Mg.1,porphin. 1-azabicyclo [5.1.0] 2,6-diketo hexan-N1-yl (12)

ΔH = 0.04763
The charge on the N-adduct was 1.239.
The first of these complexes on the metal site is lower in energy than the corresponding complex on the N-pyrrole site.
These complexes are integral reactants in the proposed synthesis. The energies of the stable complexes are shown in Table 1.

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

Molecule	MP2 hartree	ZPE (HF) hartree
proline (1)	-399.92639	0.15591
prolamide (2)	-380.07894	0.16902
2-(4-iminazoyl methanyl) aziridin-3-one (3)		

-470.85137 0.14092
Mg.1,2-(2-cyanoethyl) aziridine-3-one-1-yl (4)
-1562.81913 0.40300
Mg.1,1-azabicyclo [5:1:0] 2-imido-6-keto hexan-N1-yl.porphin (5) -1562.81340 0.40465
Mg.1,1-azabicyclo [5:1:0] 2,6-diketo hexan-N1-yl.porphin (6) -1582.68164 0.39156
Mg.1,prolamid-N1-yl.porphin (7)
-1565.24321 0.45725
Mg.1, porphin.prolamid-N1-yl (8)
-1565.20125 0.45638
Mg.1,2-(4-iminazoyl methanyl) aziridin-3-one-N1-yl.porphin (9) -1656.01574 0.42940
Mg.1,porphin.2-(4-iminazoyl methanyl-aziridin-3-one-N1-yl.porphin (10)
-1655.96813 0.42754
1-azabicyclo [5.1.0] 2,6-diketo hexane (11)
-397.51741 0.10317
Mg.1,porphin. 1-azabicyclo [5.1.0] 2,6-diketo hexan-N1-yl (12)
- 1582.63240 0.38975
pyroglutamylhistidinylprolamide (13)
-1248.66433 0.42603
Mg.1, 2-(4-iminazoyl methan-1-yl) aziridin-3-one-N1-yl.porphin.prolamid-N1-yl (14)
-2035.73478 0.61020
Mg.1,histidin-N1-yl-prolamide.porphin (15)
-2035.95706 0.60949
Mg.1, porphin.histidinyl-N1-yl-prolamide (16)
-2035.81753 0.61210
histidinylprolamide (17)
-851.03735 0.31663
Mg.1, 1-azabicyclo [5.1.0] 2,6-diketo hexan-N1-yl porphin.histidinyl-N1-yl-prolamide (18)
- 2433.21740 0.71639
Mg.1,pyroglutam-N1-yl.histidinylprolamide.
porphin (19) -2433.33380 0.72049
Mg.1,porphin.pyroglutam-N1-yl.histidinylprolamide (20) -2433.38038 0.71741
Mg.porphin (1) -1185.12250 0.29262
$OH^{\cdot}$ -75.52257 0.00911
OH^{-} -75.51314 0.00885
H_2O -76.19924 0.02148
NH_3 -56.35738 0.03529
H_2 -1.14414 0.01034

3.2 The Overall Stoichiometry for the Formation of the Tripeptide TRH

Although Mg.porphin is here taken as the catalyst for the reaction, the overall stoichiometry to form the TRH is comprised of the individual reactants to form the three stereospecific primary reactant amino-acids, as:

For the amino acid proline, [19], the prebiotic synthesis has been given where the reactants listed to make the non-zwitterionic acid may be formed from simpler gaseous molecules as,

$$H\text{-}C \equiv C\text{-}C \equiv C\text{-}H + NH_3 + CO + H_2O + H_2 \rightarrow C_5H_9NO_2$$

$$\Delta H = -0.17397 \text{ h}$$

For the amino acid histidine, [20], a prebiotic synthesis has been given where the reactants listed to make the non-zwitterionic acid may be formed from simpler gaseous molecules as,

$$NH_2\text{-}CN + H\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}H + NH_3 + CO + H_2O \rightarrow C_6 H_9 N_3 O_2$$

$$\Delta H = -0.16965 \text{ h}$$

For the amino acid glutamic acid, [21], the prebiotic synthesis has been given where the reactants listed to make the non-zwitterionic acid may be formed from simpler gaseous molecules as,

$$H\text{-}C{\equiv} C\text{-}H + 2\ HCN + H_2 + CO + 3H_2O \rightarrow C_5H_9NO_4 + NH_3$$

$$\Delta H = -0.19326 \text{ h}$$

The total stoichiometry for the formation of TRH from its immediate precursors, prolamide, 2-(4-iminazoyl methanyl) -aziridin-3-one and pyroglutamyl aziridone, each formed from essential prebiotic molecules, can then be written as,

prolamide + 2-(4-iminazoyl methanyl) aziridin-3-one + 1-azabicyclo [5.1.0] 2,6-diketo hexane →

pyroglutamylhistidinylprolamide (Fig.1)

$$C_5H_{10}N_2O + C_6 H_7N_3O + C_5H_5NO_2 \rightarrow C_{16} H_{22}N_6O_4$$

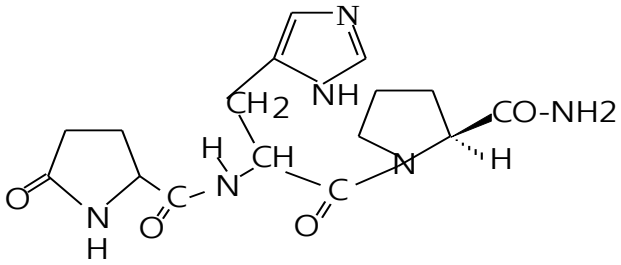


Fig.1 pyroglutamylhistidinylprolamide (13)

$$\Delta H = -0.20511 \text{ h}$$

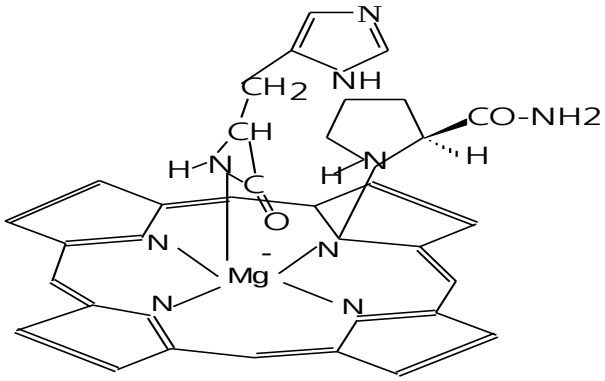
The enthalpy change for the formation of each of the aziridone precursors is negative and also the formation of the final tripeptide is negative indicating that this may be the energetically favourable route to the initial formation of the tripeptide.
The intermediates by which these stoichiometric reactions may have occurred are as follows where the first sequence involves the formation of the histidinylprolamide.

$$\Delta H = -0.10108 \text{ h}$$

3.3 The formation of Mg.1, 2-(4-iminazoyl methan-1-yl) aziridin-3-one.porphin. prolamid-N1-yl

With a vacant magnesium coordination site 2-(4-iminazoyl methan-1yl) -aziridin-3-one may form a weak charge transfer complex with Mg.porphin.prolamid-N1-yl as,

2-(4-iminazoyl methanyl) aziridin-3-one + Mg.1,porphin.prolamid-N1-yl →



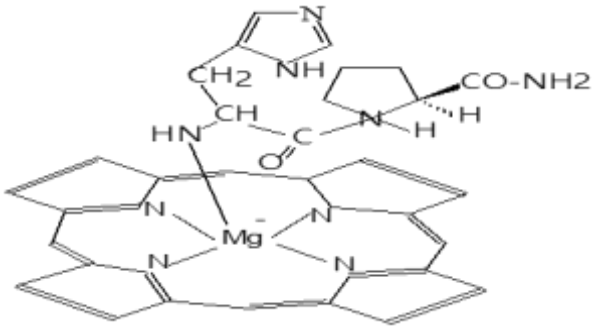
Mg.1, 2-(4-iminazoyl methan-1-yl) aziridin-3-one-N1-yl..porphin.prolamid-N1-yl (14)

$$\Delta H = 0.248966 \text{ h}$$

The di-adduct is stable and the adduct charges are: prolamide adduct 0.702, and the histidinyl adduct 0.022.
The charge of the prolamide ring nitrogen is -0.535, and that of the amide nitrogen is -0.929.
For the histidinyl adduct the aziridone nitrogen has a charge of -0.422, and the carbonyl carbon atom a charge of 0.182. These charges are commensurate with the formation of a peptide bond.

3.4 The formation of Mg.1,histidin-N1-yl. prolamide.porphin.

The two adducts may coalesce as,
Mg.1, 2-(4-iminazoyl methan-1-yl) aziridin-3-one-N1-yl..porphin.prolamid-N1-yl. →



Mg.1, histidin-N1-yl-prolamide. (15)

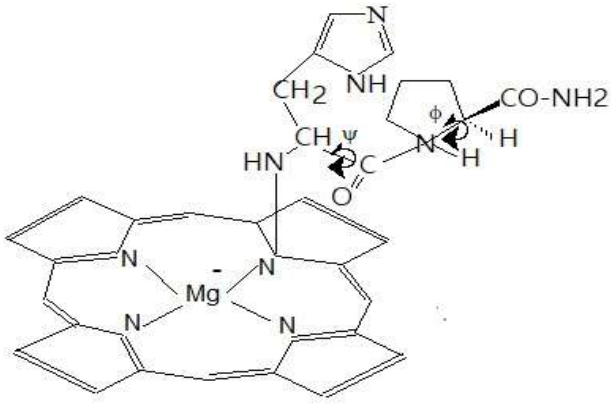
$$\Delta H = -0.22291 \text{ h}$$

The adduct carries a charge of 0.176.
The charge on the prolamide adduct ring nitrogen is -0.771 and the amide nitrogen is -0.918. The histidinyl nitrogen bound to the magnesium ion has a charge of -0.440.
The activation energy to form the peptide bond was calculated as, 0.015, whilst that for the reverse reaction was 0.241.

3.5 The formation of Mg.1,porphin. histidin-N1-yl.prolamide

The Mg.1,histidinyl-N1-yl.prolamidyl.porphin may be excited by radiation to the higher N-adduct state as,

Mg.1,histidin-N1-yl.prolamidyl.porphin →



Mg.1,porphin.histidin-N1-yl-prolamide (16)

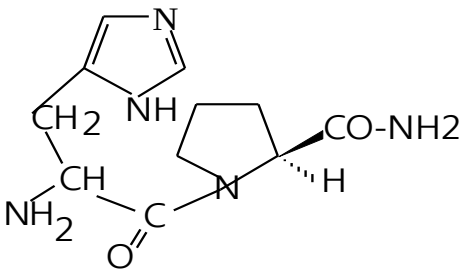
$$\Delta H = 0.14185 \text{ h}$$

The adduct carries a charge of 0.914.

At this point in the synthesis the dipeptide, histidinylprolamide could be released from the catalyst according to the equation,

Mg.1,porphin.histidin-N1-yl-prolamide + H^+ →

Mg.porphin +



histidinylprolamide (17)

ΔH = -0.34486 h

The energy for the formation of the histidinylprolamide dipeptide may then be calculated as,

2-(4-iminazoyl methanyl) aziridin-3one + prolamide → histidinylprolamide

ΔH = -0.10108 h

It is these inter amino acid bonding energies that allow the energy of a protein to be calculated where each bonding energy may be optimal from the free rotation of the added amino acid as defined by the rotation angles ψ and φ, [30]. As the adduct is present as a high energy compound it may be able to optimize the rotation angles allowing each successive amino acid generated to attain an optimal primary and secondary structure. The presence of the catalyst does not greatly affect the rotations where a slight preference for the L-amino acid monomers to form a right-handed helix is expected, [31]. For the corresponding Mg.porphin,alanylalanine^{-1}, the right-handed helix (120,120) and the left-handed helix (240,240) are of comparable energy (< 1kcal. Mol^{-1}) The left and right-handed generated helices are shown in Fig.2 for the Mg.porphin,alanylalanine^{-1} complexes.

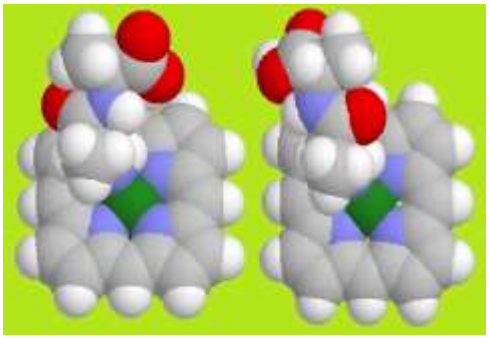


Fig. 2: Left and right-handed generated complexes of Mg.porphin,alanylalanine$^{-1.}$

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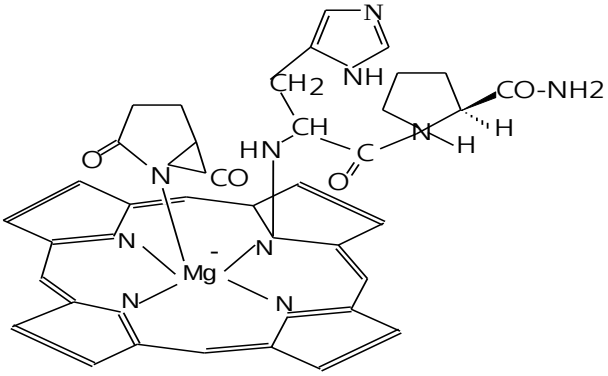
3.6 The formation of Mg.1,1-azabicyclo [5.1.0] 2,6-diketo hexan-N1-yl.porphin.histidin-N1-yl-prolamide

A bicyclo[5.1.0] 2,6-diketo hexane (11) may form an adduct with the vacant Mg.porphin binding site as,

bicycle [5.1.0] 2,6-diketo hexane (11)
+ Mg.1,porphin.histidin-N1-yl.prolamide →



Mg.1, 1-azabicyclo [5.1.0] 2,6-diketo hexan-N1-yl porphin.histidin-N1-yl.prolamide (18)

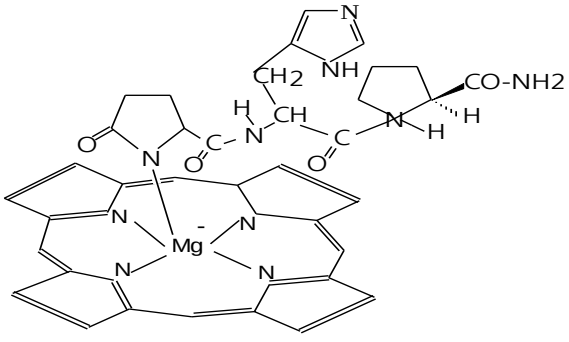
ΔH = 0.11855 h

The charge on the bicycle [5.1.0] 2,6-diketo hexane adduct was 0.827, that on the histidin-N1-yl.prolamide adduct 0.002.

3.7 The formation of Mg.1,pyroglutam-N1-yl.histidinylprolamide.porphin

The Mg.1, 1-azabicyclo [5.1.0] 2,6-diketo hexan-N1-yl.porphin.histidin-N1-yl-prolamide adducts may coalesce as,

Mg.1, 1-azabicyclo [5.1.0] 2,6-diketo hexan-N1-yl porphin.histidin-N1-yl-prolamide →



Mg.1,pyroglutam-N1-yl.histidinylprolamide. porphin (19)

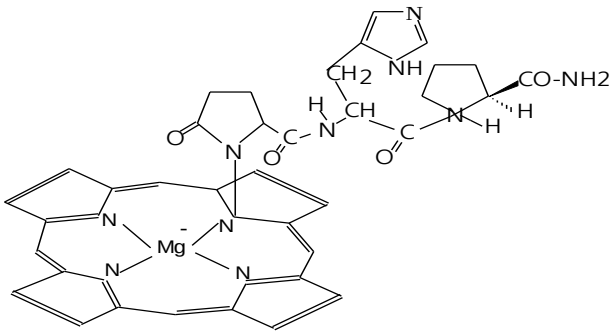
ΔH = -0.11275 h

The charge on the adduct was 0.601

3.8 The formation of Mg.1,porphin pyroglutamylhistidinylprolamide.

The Mg.1,pyroglutam-N1-yl.histidinylprolamide. porphin may be excited to a higher energy state as,

Mg.1,pyroglutam-N1-yl.histidinylprolamide. porphin →



Mg.1,porphin.pyroglutam-N1-yl.histidinylprolamide (20)

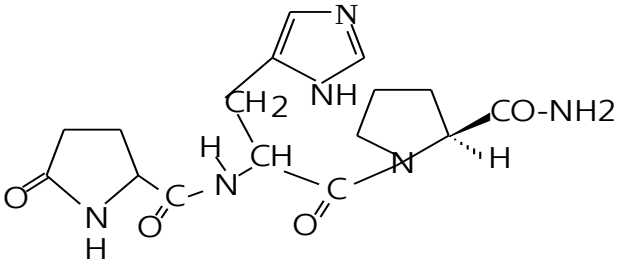
$$\Delta H = -0.04933 \text{ h}$$

The charge on the adduct was 0.0.942.

3.9 The formation of pyroglutamyl histidinylprolamide.

The reaction of the Mg.1,porphin.pyroglutam-N1-yl.histidinylprolamide with a hydrogen ion and hydroxyl anion may free the tripeptide from the catalyst as a neutral amide as,

Mg.1,porphin.pyroglutam-N1-yl.histidinylprolamide →



pyroglutamylhistidinylprolamide (13)

$$\Delta H = -0.40535 \text{ h}$$

The potential energy diagram for this peptide bonding is given in Fig.3. where the NH of histidinylprolamide adduct acts as a nucleophilic reagent to bond with the CO of the NH-bound pyroglutamyl adduct.

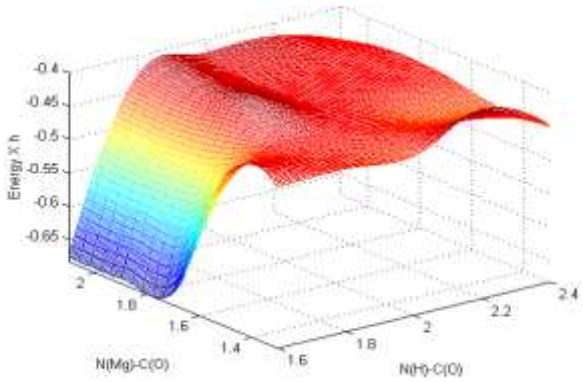


Fig. 3: The nucleophilic histidinylprolamide is near (2.4,1.6). The transition state with the electrophilic pyroglutamyl adduct is near (1.6,1.3) and the pyroglutamylhistidynylprolamide near (1.3, 2.1).

The formation of pyroglutamylhistidinyl prolamide may then be given as,

1-azabicyclo [5.1.0] 2,6-diketo hexane + 2-(4-iminazoyl methanyl) aziridin-3-one + 1-azabicyclo [5:1:0] 2-6-diketo hexane →

pyroglutamylhistidinylprolamide

$$\Delta H = -0.20511 \text{ h}$$

The activation for peptide bond formation was calculated as, 0.010 h, and for the reverse reaction as, 0.236.

4 Conclusion

The surface catalyzed photochemically activated copolymerization of the postulated prebiotic aziridone derivatives for the amino acids proline, histidine, and pyroglutamic acids provides a plausible explanation for the formation of the stereospecific tripeptide, pyroglutamylhistidinylprolamide, according to the laws of chemistry although the concentrations of these molecules and the time for their prebiotic synthesis is open to wide speculation, possibly millions of years. However, the reaction of these highly reactive molecules is assisted by the catalyst, Mg.porphin, [17], available at the time of photosynthesis, [16], providing a reduced entropy change for reaction and a lowering of the activation energy for each step in the sequence of reactions.

The mechanism used here of a co-polymerization of prebiotic aziridones would enable the formation of the possible 23^{100} different proteins for a typical poly amino acid where the enthalpy change is

favourable and the activation energy smaller than for a gas phase reaction of the free aziridones.

The high reactivity of the aziridones leads to their self initiation, propagation and termination to form polyamino acids. Although this mechanism has used the catalyst as a two-site catalyst, Mg.porphin, is really a five site catalyst well able to synthesize aziridone derivatives in situ and simultaneously form multiple growing peptides in a higher energy state on its surface, and thereafter enable the mutual termination of peptides to produce cyclic peptides such as gramicidin S, [32]. Enzymes containing the catalyst such as cytochrome-c do suggest that this mechanism occurred, [33].

The aziridones are possible precursors of the tRNAs, [11], of present biochemistry as highly reactant with the 3' OH groups of RNAs.

The co-polymerization of aziridones is expected to yield life changing industries in synthetic protein and bio-degradable plastics.

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

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References:

[1] Computer-assisted modeling: Contributions of computational approaches to elucidating macromolecular structure and function. National Research Council (US) Committee on Computer-Assisted Modeling.Washington (DC): *National Academies Press (US)*; 1987.

[2] M.Yčas, Computing tertiary structures of proteins. *J Protein Chem*. 9, 1990, pp. 177–200.

[3] K. Nishikawa, T. Ooi, Y. Isogai, N. Saitô, Tertiary structure of proteins. I. Representation and computation of the conformations, *Journal of the Physical Society of Japan*, 15, Vol. 32, No. 5, 1972, pp. 1331-1337.

[4] D. Kutntz, G. M. Crippen, P. A. Kollman and D. Kimelman, Calculation of Protein Tertiary Structure, *J. Mol. Biol*. 106, 1976, pp.983-994.

[5] D. B. Singh and R. K. Pathak, *Bioinformatics: Methods and Applications*,Ed. Academic Press, 2021

[6] Z. Wang, Y. Han, J. Li and X. He, Combining the fragmentation approach and neural network potential energy surfaces of fragments for accurate calculation of protein energy, *J. Phys. Chem. B*, 2020, 124, 15, pp.3027–3035.

[7] T.M.Birshtein and O.B. Ptitsyn, *Conformations of Macromolecules*, Interscience Publ. N.Y. 1966.

[8] H.A.Scheraga,R.A.Scott, Gvanderkooi, S.J.Leach, K.D.Gibson, T.Ooi and G.Nemethy, in *Conformations of Biopolymers*. Ed..G.N. Ramachandran, Academic Press.1967. pp.81-105.

[9] R.Guillemin, Hypothalamic hormones: releasing and inhibiting factors. *Hos. Pract*. 1973.

[10] A.V.Schally, A.Arimura, and A.J.Kastin, Hypothalamic Regulatory Hormones, *Science*, 179, 1973, pp. 341-350.

[11] A.L.Lehninger, *Biochemistry*, Worth, New York, 1975, pp. 356.

[12] E. Fröhlicha and R.Wahla, The forgotten effects of thyrotropin-releasing hormone: metabolic functions, *Frontiers in Neuroendocrinology*, 52 ,2019, pp. 29–43.

[13] R. Bílek, TRH-like peptides in prostate gland and other tissues (short survey), *Physiological Research*, 49,1, 2000, pp. S19-S26.

[14] N. Aylward, and N.R.Bofinger, Possible origin for porphin derivatives in prebiotic chemistry - a computational study, Orig.Life Evol. Biosph. vol.35(4), 2005, pp. 345-368.

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

[16] R. Hooper, Revealing the dawn of photosynthesis, *New Scientist*. 2006

[17] 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,

[18] N. Aylward, The Synthesis of Terpenes in Prebiotic Molecular Evolution on Earth. *WSEAS Int. Conf. on Biomedical Electronics and Biomedical Informatics*. Rhodes Island, Greece, August 20-22, 2008,. pp. 202-207.

[19] N.Aylward, A Computational Study of a Prebiotic Synthesis of L-Leucine, L-Isoleucine and L-Proline, *WSEAS Transactions on Biology and Biomedicine*, Vol.12, 2015, pp. 87-103.

[20] N. N. Aylward, A computational study of a prebiotic synthesis of L-histidine, in WSEAS Proceedings of the 15 th. International

Conference on Computers,. Eds. N.Mastorakis et.al.Rhodes, Greece, 2011, pp.166-171,

[21] N.Aylward, A Computational Study of a Prebiotic Synthesis of L-Asparagine, L-Aspartic Acid, L-Glutamine and L-Glutamic Acid, *International Journal of Biology and Biomedical Engineering*, 8, 2014, pp. 142-150.

[22] T. Gleede, L.Reisman, E.Rieger, P.C.Mbarushimana, P.A. Rupar and F.R. Wurm, Aziridines and azetidines: building blocks for polyamines by anionic and cationic ring-opening polymerization, *Polym. Chem.*,10, 2019, pp, 3257-3283.

[23] Ed.A.K.Yudin, *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, 2006.

[24] *Gaussian03, Users Reference*, Gaussian Inc.,Carnegie Office Park, Bldg.6., Pittsburgh, PA 15106, USA,2003.

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

[26] 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.

[27] IUPAC Nomenclature and Symbolism for Amino Acids and Peptides, *Eur . J . Biochem* . 138. 1984, pp. 9-37.

[28] E.H.Rodd, *Chemistry of Carbon Compounds*, Vol.1B. Elsevier Publ.Comp.1952, p. 1116.

[29] J.P.Collman, L.S.Hegedus, J.R.Norton, R.G. Finke, Principles and Applications of Organotransition Metal Chemistry, *University Science Books*, Mill Valey, California, 1987.

[30] D.Mansuy,J.P.Battioni, D.Dupree, E.Santoni, *J.Am. Chem. Soc*.104, 1982, pp. 6159-6161

[31] P.J.Flory in G.N.Ramachandran, Ed., *Conformations of Biopolymers, Configurational statistics of polypeptide chains*. Academic Press.Vol.1, 1967, pp. 339-363.

[32] S. E. Hull, R. Karlsson, P. Main, M. M. Woolfson and E. J. Dodson, The crystal structure of a hydrated gramicidin S–urea complex, *Nature* volume 275, 1978, pp. 206–207.

[33] R.E.Dickerson and I.Geis, *The Structure and action of proteins*. N.Y.Harper and Row, 1969.

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Conflict of Interest

The authors have no conflict of interest to declare.