THE UNEXPECTED FINDING OF FORMATION OF AN AROMATIC INTERMEDIATE IN A PREBIOTIC PHOTOREDUCTION

CHAPTER 5
Chapter 5

The unexpected finding of formation of an aromatic intermediate in a prebiotic photoreduction.

ABSTRACT: In this chapter we present the role of aromaticity in a very unusual place, the chemistry of origin of species. The reaction we mentioned in this chapter involves a very primordial step for evolution of biomolecules. We have shown how aromaticity dictates the unusual dimerization of two anions to give a dianionic intermediate. The dimerization of anions is unfavorable due to electrostatic repulsion. Yet such a dimerization is shown to occur due to the gain in aromaticity of formed six-membered cyclic intermediate. We also report the rare case of PCET/HAT in an aromatic intermediate which happens to be quintessential for the primordial reduction step.
5.1. Introduction

As we all know HCN is a linear triatomic molecule having a high dipole moment. Being itself considered to be one of the most toxic compound known to man, it also plays a distinctive role in the prebiotic origin of life.[1-3] HCN is considered to be the ancestral molecule for the basic building blocks of life, i.e. DNA, RNA and sugars by most relevant hypotheses.[3-8] Moreover, HCN being substantially present in interstellar space, cosmic gas clouds and comets makes it an even stronger contender for the most viable earliest feedstock molecule for prebiotic synthesis of life sustaining molecules.[9-11] Radiolysis experiments of aqueous solutions of HCN and other cyanides have demonstrated the formation of prebiotic molecules like nucleobases and amino acids for several decades.[12-14] These radiolytic experiments owing to their use of high energy radiation loses selectivity of products with polymer formations and hence are incapable of rendering any real mechanistic insights. Recently based upon similar concepts, using a novel approach, Sutherland and co-workers have shown that photolytic disproportionation of 1 leads to formation of sugar building blocks like glycoaldehyde (2) and glyceraldehydes (3).[15] This work forms a part of an elegant set of experiments carried out by Sutherland and co-workers to strengthen the RNA world hypothesis.[15-17] The route for primordial synthesis of Nucleotide has posed a challenge to chemists for years and to the viability of the RNA world hypothesis.[3] Significant amount of efforts have been directed towards the development of one-pot synthesis strategies for nucleotides. The detailed understanding of probable
mechanistic pathways for the formation of nucleotide under prebiotic conditions, can enable us to have a knowhow of the pathways of RNA formation on prebiotic earth.\textsuperscript{[15-18]} The recent works of Sutherland and co-workers have experimentally demonstrated a new plausible prebiotic route for synthesis of nucleotides, bypassing the more commonly accepted idea that nucleotides have been synthesized from free sugar and nucleobases, by establishing the fact that synthesis of nucleotides can be possible from a common chemical predecessor.\textsuperscript{[16]} The production of sugar antecedents of pentose upon photolytic reduction of 1 using cyanometallates has established the hypothesis that ribonucleotides could have formed on their from simple inorganic/organic molecules under prebiotic earth conditions.\textsuperscript{[15]} A reduction of the nitrile bond in 1 is believed to be a crucial step in prebiotic chemistry by most hypotheses. The mechanism for the formation of purine bases and its precursors from 1 has been investigated and reported recently using quantum chemical computations,\textsuperscript{[19]} the exact mechanism for reduction of the nitrile bond of 1 upon photolysis/ radiolysis facilitating the formation of small molecules significant to the prebiotic chemistry has been unknown to researchers for over five decades. The present understanding is that reduction of 1 in the photoredox processes proceeds through the formation of Methaniminyl radical (H$_2$C=N$^*$), which has been detected experimentally during radiolysis of aqueous solution of 1.\textsuperscript{[18]} Methaniminyl radical has also been proposed by Sutherland et al to be the key intermediate in the synthesis of sugar precursors, formed upon photoreduction of an aqueous solution of HCN.\textsuperscript{[15]} However, in this chapter we report the possibility of an unique pathway, using theoretical techniques, for photolytic reduction of nitrile bond of 1, which proceeds through the initial...
formation of molecular dipole bound anions. The dipole bound are observed to be formed by attachment of electrons formed due to the photo excitation of a metallic cyanometallate. The dipole bound anions initiate an unanticipated chain of chemical reactions, ultimately leading to the reduction of the nitrile bond of 1, avoiding the formation any neutral radicals like (H₂C=N\textbullet) along the pathway, as is popularly believed.[15,18,20] The strength of this unique mechanistic pathway lies in its ability in explaining the reduction of the nitrile bond 1 in the presence of solvated electrons in water produced either from photoredox reagent or radiolysis or from any other source.

Fermi in the year 1947 proposed the probable existence of Dipole bound anions on theoretical grounds.[21] The general rule of the thumb, within the limitation of the Born-Oppenheimer Approximation, is that a molecule can bind an electron to form a bound state if it has a higher than 2.5 D.[22,23] The solvation of electrons by water clusters and attachment of electron DNA is connected to the chemistry of dipole bound anions and have been rigorously studied on both experimental and theoretical, and dipole bound anion can have the central role to play for most electron driven reactions in aqueous medium.[24-28] DNA strand breaks have been suggested to happen via electron attachment to DNA and formation of dipole bound anionic states.[28] Despite the fact that dipole bound anions have been investigated thoroughly by theoretical and experimental works, [22-28] it has never been implicated to trigger a cascade of chemical reactions leading to synthesis of complex molecules from simpler ones.[29] We report in this chapter on the basis of quantum chemical techniques and \textit{ab initio} molecular dynamics, previously unknown reaction paradigm, initiating from
dipole bound anions in doublet spin state (S=1/2) transforming into valence bound molecular radical anions, followed by an unprecedented incident of proton coupled electron transfer (PCET) or more precisely a hydrogen atom transfer (HAT)\textsuperscript{[30]} occurring from one molecular radical anion species to another. The reaction is at first initiated by the association of two radicaloid anions to form a transient singlet spin state (S=0) dianionic entity in aqueous environment leading to the pairing of the electrons. The dimer of the valence bound anions, which itself is in a dianionic state, is characterized to be an aromatic intermediate. This aromatic stabilization has been shown to be the basis of the dimerization of two anions despite their Columbic repulsion. The dimerization of the valence bound anions is followed by a hydrogen atom transfer or PCET within the dianionic entity resulting in dissociation into two singlet anionic species, thus in a sense achieving the reduction of the nitrile bond in HCN. This case of “PCET extraordinaire” is shown to occur also in subsequent reactions involved in the formation of the fragments of sugars from 1. The reduction mechanism reported in this chapter based upon theoretical studies have broader implication in other solvated electron facilitated reductions.

5.2. Results and Discussion

Sutherland et al. had shown that the reduction of nitrile bond 1 can be facilitated by photo-activation of photoredox agent and subsequently to sugar precursors selectively, as contrary to radiolytic experiments that produce myriad products,\textsuperscript{[15]} This observation has been investigated on the quantum chemical and molecular dynamics studies. The experiment by Sutherland et al. comprised of irradiation of a photoredox reagent, [Cu(CN)\textsubscript{3}]\textsuperscript{2-} (4) in an aqueous solution of 1 using 254 nm light,\textsuperscript{[15]}
The observations were explained hypothesizing that the irradiation of the photoredox reagent lead to transfer of electron transfer into the solution, subsequently generating \( \text{H}_2\text{C}=\text{N}^\bullet \) radical from aqueous solution of 1 which carried out the further chain of reactions. Using B3LYP optimized geometry, the \( S_0-S_1 \) vertical excitation energy of 4 was computed to be 265 nm using N-electron Valence 2\(^{\text{nd}}\) order Perturbation Theory (NEVPT2) and continuum solvent model, COSMO incorporated to account for solvent effects. These findings suggest towards the possibility of excitation of 4 from its \( S_0 \) to its \( S_1 \) state upon irradiation with the experimentally used light. Transition metal species by the virtue of their heavy atomic number is likely to undergo intersystem crossing from the excited \( S_1 \) state to the triplet \( T_1 \) state (see Figure 1).\(^{[31]}\) Based upon DFT computations we observed that the Cu centre of 4 could not bind \( \text{H}_2\text{O} \) or 1 acting as ligands, or in other words was incapable of increasing its coordination number in its ground electronic \( S_0 \) state. Strangely enough, we observed that 1 could coordinate to the Cu centre in 4 in the \( T_1 \) state and \( S_1 \) state. Hence we shifted our focus and optimized the \( T_1 \) state of 4 with B3LYP and MP2(Moller Plesset 2\(^{\text{nd}}\) order perturbation theory. The \( T_1 \) state 4 was found to be able to bind 1 or a molecule of water within its coordination sphere (see Figures 1 and 2). Computations predicted the binding of 1 to \( T_1 \) state of \([\text{Cu(CN)}_3]^2(\cdot)\) be favorable by 28 kcal/mol. The striking feature turned out to be one of the SOMOs of the triplet \([\text{Cu(CN)}_3(\text{HCN})]^2(\cdot)\) (5) which was found to bear a remarkable similarity to that of a dipole bound anion \([\text{HCN}]^\text{(-)}\) (See Figures 1 and 2). Thus we investigated the possibility that if 5 could produce a dipole bound anion upon dissociation. The dissociation of \([\text{Cu(CN)}_3(\text{HCN})]^2(\cdot)\) in its triplet state into two doublet species : (a) a dipole bound anion, \([\text{HCN}]^\text{(-)}\) (7) and (b) a doublet \([\text{Cu(CN)}_3]^\text{(-)}\)
(6) species was found to happen through transition state, $\text{TS}_{5-6-7}$ (see Figure 2(B)). The transition state $\text{TS}_{5-6-7}$ was optimized at both DFT(B3LYP) and MP2 level of theory and the dissociation was found to be slightly exoergic ($\Delta G = -1.2$ kcal/mol). The free energy activation barrier of $\text{TS}_{5-6-7}$ for the dissociation with respect to the optimized energy of $T_1$ state of 5 was computed to be 13.9 kcal/mol at MP2(CPCM)/B1 level of theory. We were convinced from these computations that what Sutherland and co-workers mentioned as solvated electron or electron being ejected out by UV radiation was essentially the organometallic complex 5 ejecting an electron, and getting transported via a molecular vehicle, in this case 1 having enough high dipole moment to form a dipole bound anion.
Figure 1. The steps of photo redox cycle of Cu(CN)$_3^{2-}$ leading to the formation of dipole bound anion, [HCN]$^\cdot$. 
Figure 2. (A) The MP2/B1 optimized structure of $[\text{Cu(CN)}_3(\text{HCN})]^2(-)$ intermediate in its $T_1$ state. (B) The diffuse SOMO and MP2/B1 optimized structure of the transition state TS$_{5-6,7}$ of evolution of $[\text{HCN}]^(-)$ from $[\text{Cu(CN)}_3(\text{HCN})]^2(-)$ in its triplet state. (C) The diffuse SOMO of the HCN minus. (D) The MP2/B1 optimized structure of $[\text{Cu(CN)}_3(\text{HCN})]^2(-)$ intermediate with one $\text{H}_2\text{O}$ hydrogen bonded to the proton of HCN. (E) The MP2/B1 optimised structure of the TS of evolution of HCN$^(-)$ dipole bound anion with one water hydrogen bonded to the proton.
of HCN. Colour coding of atoms: Cu: Orange, N : Blue, O: Red C: Greyish Black, H: White. The black arrows show the displacement vector along imaginary mode frequency in transition state. Important interatomic distances are indicated in Å.

The aforementioned mechanism can be generalized to be one of the possible pathways that reduction is achieved by photoredox reagents. The possibilities for formation of H$_2$C=N• radical from 5 were thoroughly investigated in an unbiased manner, and all attempts lead to dead ends. One of the possible routes that we investigated for the formation of the H$_2$C=N• radical by protonation of dipole bound anion 7 on its carbon or the nitrogen by the abundant proton source around it i.e. H$_2$O and also 1. The thermodynamically unfeasible of the above mentioned process (see Figure 3 (A) to (D)) along with the absence of locatable transition states enabled us to negate the possibility of formation of H$_2$C=N• radical on strong logical grounds. Furthermore, upon investigating the reactions issuing from the interaction of HCN with 7’(the valence bound anionic form of [HCN](-)), we found that any pathway for the formation of imine involving H$_2$C=N• or HC=NH•, as an intermediate, encounters extremely unfavorable thermodynamics and kinetics. (Please See, Figure 4 and Figure 5).
Figure 3. The $\Delta E$ changes for various reaction channels starting from $[\text{HCN}]^\cdot$ at MP2(CPCM)/aug-cc-pVTZ level of theory.
**Figure 4:** The possible route of reduction of HCN by one HCN (-) valence bound anion and HCN. As the above figure shows the energetics for the above process is highly unfavorable wrt to the mechanism proposed in this manuscript.

Thus the possibility that the reaction might happen through some unexplored pathway came to our mind (see Figure 3 (E)). When gas phase geometry optimizations of [HCN](-), with two water molecules in the primary solvation sphere, was carried out using MP2/aug-cc-pVDZ and MP2/aug-cc-pVTZ, by observing the SOMO we found that indeed a dipole bound anion, 7 with two water molecules hydrogen bonded to it was being formed (see Figure 6). A valence bound anionic state, 7' having a bent HCN moiety with the proton of a water molecule interacting with the C centre...
and another H$_2$O unit staying H-bonded to the N centre was obtained upon optimization along with that (see Figure 6).

**Figure 5**: The possible route of reduction of HCN by one HCN (\(-\)) valence bound anion and HCN. As the above figure shows the energetics for the above process is highly unfavourable wrt to the mechanism proposed in this manuscript.
The geometry of these two varying forms of the anion existed even after adding extra electron and optimizing them. Single point computations at MP2(CPCM)/aug-cc-pVTZ level of theory were carried out and they revealed that the energy difference between 7 and 7’ is only 1.2 kcal/mol upon zero-pint corrected total, with 7’ found to be slightly more destabilized than 7. Hence one can consider 7 and 7’ to be almost isoenergetic in practical terms and interconversion from one form to another seemed to be quiet feasible. The two different anionic forms have distinctly different geometries. The existence of the dipole bound anionic state in bulk water was also confirmed by Molecular Dynamics. As predicted by MP2(CPCM)/aug-cc-pVTZ//MP2/aug-cc-pVTZ levels of theories, the isomeric forms would be available in aqueous medium.
Figure 6. (A) MP2(CPCM)/aug-cc-pVTZ optimised geometry of 7 with one water. (B) MP2(gas phase)/aug-cc-pVTZ optimised geometry of 7 with two water. (C) MP2/aug-cc-pVTZ optimised geometry of 7’ with two water molecules (the gas phase values are given in parenthesis). (D) The SOMO of valence bound anion 7’ with two water molecules. (E) MP2(CPCM) aug-cc-pVTZ optimised geometry of dianionic intermediate 8, microsolvated by four water molecules. (F) MP2(CPCM)/aug-cc-pVTZ optimised geometry of dianionic TS_{8-9} of the unique PCET, micro-solvated by four water molecules. The black arrows show the displacement vector along imaginary mode frequency in transition state. Colour coding of atoms: N: Blue, O: Red, C: Greyish Black, H: White. Important interatomic distances are indicated in Å.
Figure 7. (A) The MP2(CPCM)/aug-cc-pVTZ optimised geometry of dianionic intermediate 8. (B) MP2(CPCM)/aug-cc-pVTZ optimised geometry of dianionie TS of the unique PCET. (C) The Molecular Orbital picture of the dianionic dimer of HCN 8 as shown in (A). Colour coding of atoms: N : Blue, C: Greyish Black, H: White. The black arrows show the displacement vector along imaginary mode frequency in transition state. Important interatomic distances are indicated in Å.
Numerous studies on theoretical and experimental have been reported with microsolvated forms of \([\text{HCN}]^-\) which have one and two water molecules H bonded to it. No report of any chemical reaction that passes through a dipole bound anion, like \([\text{HCN}]^-\) or any other has never been studied.\[^{22,23}\] Furthermore the possibility of presence of \([\text{HCN}]^-\) in the condensed or solvated phase was never been suggested by any form of studies.\[^{22,23}\] The SOMO of the valence bound anionic form of \([\text{HCN}]^-\), \(7'\) which upon investigation was seen to be (see Figure 6(D)) largely localized and centered on the HCN moiety in contrast to diffuse SOMO of the water solvated dipole bound anion which is delocalized over large external region (Please see Figure 8). The SOMO of \(7''\) was found to be largely composed of contributions from the pi antibonding orbital of the nitrile bond.

**Figure 8.** The SOMO \(\text{HCN}^-\) with a water molecule coordinated to the proton of HCN, clearly depicting the distribution of the electron over a diffuse orbital indicating the formation of dipole bound anion.
Molecular species having individual unpaired electrons have a tendency to pair up and form in effect closed shell singlet species, and hence we explored the coupling of two dipole bound anions or valence bound anion radicals. Surprising we found that indeed two valence bound anions (7') can dimerize and lead to the formation of a closed shell intermediate, a dianionic dimer (8) (see Figure 6 and Figure 7 (A)). We observed that, as expected, the two anions (7') experience strong electrostatic repulsion, when brought together in vacuum. Hence, the chances for formation of such dimer in gas phase is highly unfavourable, and is found to be exoergic by 34 kcal/mol (free energy change at the MP2/aug-cc-pVTZ level of theory). Interestingly the situation changes drastically in water, and due to the high dielectric constant of water (~78), the Coulombic repulsion gets screened significantly with the dimerization becoming significantly favourable. The dimerization of 7' is a barrier less process which results in substantial stabilisation upon formation of dimer 8, having a total energy change of, $\Delta E = -36$ kcal/mol and the corresponding free energy change of, $\Delta G = -24.6$ kcal/mol at MP2(CPCM)/aug-cc-pVTZ. The geometry of 8 has been thoroughly investigated and optimized with multiple electronic structure methods within the single reference manifold. The structure of 8 is predicted to be symmetric upon optimization of geometries at MP2(CPCM)/aug-cc-pVTZ. The optimizations were both carried out with and without explicit water molecules and all these unanimously predict the symmetric structure for 8 (see Figure 6 and Figure 7(A)). Additionally, the electronic structure of 8 has been investigated thoroughly with CASSCF and was found to be consistently single reference thus further validating our use of MP2 and DFT methods for optimization and analysis. Upon investigation of the
The electronic structure of 8, which forms upon dimerization of two molecular anions, observed that it possesses very interesting properties. When the molecular orbital of 8 were plotted and investigated, we observed the presence of heavy delocalization of extensive π orbitals (see Figure 7 (C)) and the presence of aromaticity has been implicated. Nucleus Independent Chemical Shift (NICS) which is the primary tool used to study aromaticity reveals that 8 is aromatic (see Table 1 for NICS data details and comparison with benzene). 8 acts as the stepping stone to a cascade of reactions. The optimized geometry of 8 reveals that the hydrogen from each [HCN] \(^{(1)}\) unit is interacting with the N atom of the other unit.

Table 1. Comparison of magnetic aromaticity by the NICS method of [HCN] \(_2^{2(\cdot)}\) and Benzene at the DFT/B3LYP level of theory.

<table>
<thead>
<tr>
<th>Species</th>
<th>DEF2TZVP</th>
<th>DEF2TZVP</th>
<th>DEF2QZVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>[HCN] (_2^{2(\cdot)})</td>
<td>C(_6)H(_6)</td>
<td>C(_6)H(_6)</td>
<td>C(_6)H(_6)</td>
</tr>
<tr>
<td>NICS(0)(_{iso})</td>
<td>-22.3</td>
<td>-8.2</td>
<td>-22.2</td>
</tr>
<tr>
<td>NICS(1)(_{iso})</td>
<td>-36.5</td>
<td>-29.3</td>
<td>-36.6</td>
</tr>
<tr>
<td>NICS(1)(_{iso})</td>
<td>-15.4</td>
<td>-17.4</td>
<td>-15.4</td>
</tr>
</tbody>
</table>

The H-N bond distance of intermediate 8 was computed to be around 1.50 Å. This happens to be much shorter as compared to the N-H H-bond distance, providing evidence that the interaction between N and H to more covalent bond rather than of a simple H-Bonding interaction. The C-N bond distance for the dianion 8 was found to be 1.26 Å, and is longer than the C-N nitrile bond in H-CN. The geometry of
[HCN]$_2^{2(-)}$ was also optimized at MP2(CPCM)/aug-cc-pVTZ level of theory without having explicit water molecules. We found that the geometrical parameters were almost identical to those of 8. We computed the Vertical Detachment Energies (VDE) of 8 at various levels of theory and found out that the dianionic intermediate 8 behaves as a two electron trap (see Table 2). Thus 8 behaving like a transient two electron trap (see Table 1) facilitates the formation of the significantly stable singlet closed shell dianionic species.
<table>
<thead>
<tr>
<th>Species</th>
<th>Method</th>
<th>1st e\textsuperscript{-} Vertical Detachment Energy (eV)</th>
<th>2nd e\textsuperscript{-} Vertical Detachment Energy (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[(HCN)\textsubscript{2}\textsuperscript{2(-)}.4H\textsubscript{2}O]</td>
<td>RO-MP2/CPCM/aug-cc-pVTZ (Solvent=Water)</td>
<td>3.76</td>
<td>9.37</td>
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<td>[(HCN)\textsubscript{2}\textsuperscript{2(-)}.4H\textsubscript{2}O]</td>
<td>U-MP2/CPCM/aug-cc-pVTZ (Solvent=Water)</td>
<td>4.44</td>
<td>9.35</td>
</tr>
<tr>
<td>[(HCN)\textsuperscript{1(-)}.2H\textsubscript{2}O]</td>
<td>U-MP2/CPCM/aug-cc-pVTZ (Gas Phase)</td>
<td>-0.12</td>
<td>-</td>
</tr>
<tr>
<td>[(HCN)\textsuperscript{1(-)}.2H\textsubscript{2}O]</td>
<td>U-MP2/CPCM/aug-cc-pVTZ (Solvent=Water)</td>
<td>3.08</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2. Vertical Detachment energy in eV of the anionic states of the HCN and HCN dimer [(HCN)$_2$]$^{(-)}$, computed on geometry optimized at MP2(CPCM)/aug-cc-pVTZ level of theory.

Figure 9. Steps for reduction of nitrile bond of HCN and PCET to form H$_2$C=NH and HCHO subsequently forming glycine nitrile and cyanohydrins

The PCET in 8 happens through transition state TS$_{8-9}$ leading to the formation of CN$^{(-)}$ and [HC=NH]$^{(-)}$ (9), both singlet closed shell anions (See Figure 9). The barrier of the PCET was computed at MP2(CPCM)/aug-cc-pVTZ and CCSD(T)(CPCM)/aug-cc-pVTZ//MP2(CPCM)/aug-cc-pVTZ level of theory. We found the process to be practically barrierless (less than 0.5 kcal/mol) using both the theories. 9 being a
reactive anion can easily abstract a proton from the neighbourhood of solvating water molecule and form \( \text{CH}_2=\text{NH} \) (10) and \( \text{OH}^- \).

Affirmation of the above findings from static quantum chemical techniques were further obtained by conducting Born-Oppenheimer molecular dynamics (BOMD) and Car-Parrinello molecular dynamics\[^{[32]}\] (CPMD) simulations. Initially we conducted BOMD simulations using the M06-2X functional and starting from the geometry obtained from MP2 (CPCM) optimizations of the dianionic intermediate having 4 water molecules hydrogen bonded to it in the primary solvation sphere. Within 15 femtoseconds the simulation revealed that the PCET occurs, forming \( \text{CN}^- \) and \( \text{CN} \) followed by the proton abstraction to form \( \text{CH}_2=\text{NH} \) (10). Additionally, to capture the event of PCET in bulk aqueous environment we resorted to using CPMD simulations, \[^{[33]}\] within the periodic boundary condition to mimic the extended bulk system and PBE functional (DFT approach). The advantage of CPMD simulations are that it not only does include thermal fluctuations but additionally accounts for a more realistic solvation scenario. The geometry of 8 solvated by 4 water molecules was placed in a periodic cubic cell of size 12.020 \( \times \) 12.020 \( \times \) 12.020 Å\(^3\) and solvated with a total of 57 water molecules (See Figure 10 and Figure 11 ).\[^{[34]}\]
Figure 10: Snapshots of the CPMD simulation with two HCN starting from the dianion intermediate geometry but without two electrons, ie, neutral, showing absence of PCET and two HCN units flying apart. (a control simulation).

The additional negative charges due to the presence of dianion 8 was balanced by incorporating two extra protons in the simulation box. Gratifyingly we observed that in mere 50 femtoseconds the proton coupled electron transfer occurred and one of the hydrogen was transferred from one unit of $[\text{HCN}]^(-)$ to another leading to the formation of $\text{CN}^(-)$ and $[\text{CH}=\text{NH}]^(-)$. Subsequently we observed that a proton transfer from a water occurred, thus allowing the transformation of $[\text{CH}=\text{NH}]^(-)$ anion to $\text{CH}_2=\text{NH}$. Interestingly, a water molecule takes part in transfer of proton to C center rather than any hydronium, Zundel or Eigen cation. As a precautionary step when an additional calculation was performed without inclusion of two additional protons to neutralize the dianionic charge, we obtained the same results.$^{[34]}$ 10, being an imine is
known to easily undergo acidic hydrolysis forming formaldehyde $\text{H}_2\text{C}=\text{O}$ (11). Thus the set of unique molecular phenomenon, presented in this chapter reasonably clarifies the intricacies involved in the reduction of the nitrile bond of HCN to form 10 and 11.

Figure 11. The snapshots taken from the CPMD calculation starting from the dianion intermediate followed by PCET and subsequent proton take up from aqueous medium. Colour coding of atoms - H: White, C: Grey, N: Blue, O: Red.

As the theoretically unraveled pathway of nitrile bond reduction involves the dimerization of two radical anions, the question of statistical probability, for the event to occur in a condensed phase, would come into being, as radical anions would be
present in rather low concentrations. However the theoretical computations unequivocally establish the process of dimerization of two $[\text{HCN}]^{(1)}$ to be highly favorable both thermodynamically and kinetically. The photoredox reagent $[\text{Cu(CN)}_3]^{2(-)}$ being a single electron redox reagent $^{[15]}$ implicates towards the likelihood of formation of a doublet species ($S=1/2$) in solution when photo irradiated. The final products formed upon photo reduction of HCN happen to be all closed shell singlet ($S=0$) molecules. This suggests that two radicals i.e. ($S=1/2$) with doublet spin must couple with one another and effectuate formation of singlet species. Thus intuitively one can think or suggest that once enough radicals have accumulated in the solution and reached a critical concentration, then only the dimerization can happen and hence reduced product would come into being. Indeed, the experimental work by Sutherland and co-workers also reports that the first signatures indicating the formation of cyanohydrins appear a well 30 minutes after initiation of the reaction procedure and is evident from in situ $^{13}$C NMR signals. Thus the computational finding we report in this chapter nicely fits the experimental observations reported by Sutherland et al.

In addition to the CPMD simulation, BOMD simulations performed on 8 which has been microsolvated by four $\text{H}_2\text{O}$ molecules with the whole system carrying a total charge of -2 and singlet spin, reveals similar results. When charge analysis was carried out on the snapshot geometries from the BOMD simulation 8, having additional four water molecules along with two protons to electrically neutralize the system, the sum of Mulliken charges of the atoms constituting the structure HCN dimer was found to be -1.77e (NBO charges -1.8e). This vividly points towards the charge localization on
and by the HCN dimer, which happens to be essential for facilitating the formation of 9 and CN\(^{(−)}\). When a control CPMD simulation was carried out on a neutral system having the dianionic dimer 8’s geometry placed in a box of similar water molecules but without any additional proton and S=0, essentially to mimic the absence additional electron, we observed that the structure of 8 disintegrated without any reaction and two HCN molecules diffusing away from each other. This particular finding may indicate towards the possibility that upon release of two electrons into the aqueous medium, two HCN molecules which happens to be in each other’s vicinity can act as a dielectron trap and lead to the formation of the key intermediate 8.

10 can suffer a nucleophilic attack by a CN\(^{(−)}\) followed by protonation, leading to the formation of glycine nitrile (12). Formaldehyde, 11 on the other hand can be converted to cyanohydrin (13) by a nucleophilic attack of CN\(^{(−)}\). Interestingly we found that the role of dipole bound anions is not limited to the reduction of 1 leading to formation 10 and 11. Upon further investigation, we found that electron attachment to 12 and 13 can explain their observed reduction trends. Both 12 and 13, having considerably high dipole moment, forms dipole bound anions just like 1 by surmounting a low activation energy barrier. The SOMO of the cyanohydrin anion and glycine nitrile anion bears remarkable similarity to the SOMO of [HCN]\(^{(−)}\) anion (see Figure 12(A) and (B)). Much like [HCN]\(^{(−)}\) anion, these dipole bound anions also transform to their respective valence bound anions. The dipole bound anionic form of 13, which we call here as, 14 surmounts a low barrier involving a single bond rotation as it converts into a valence bound anionic state, 15. This isomerization of 13 to 15 unravels the possibility for a
intramolecular PCET from the O end to the nitrogen of the nitrile bond through TS$_{15-16}$. This crucial PCET constitutes the initiating step for the reduction of the nitrile bond in 13. The free energy barrier for this crucial intramolecular PCET for 13 is a mere 15.8 kcal/mol. To our surprise an analogous PCET involving the dipole bound anion of 12 was computed to have a steep barrier of 33.8 kcal/mol (see Figure 12 (C) and (D)). Thus difference in fate of 13 and 12 as observed by Sutherland et al owes its origin to the respective free energy barriers of this particular PCET.

Figure 12. (A) The diffuse SOMO of mono anionic state glycinenitrile (dipole bound anion). (B) the diffuse SOMO of mono anionic state of cyanohydrin (dipole bound anion) (C) The MP2(CPCM)/aug-cc-pVDZ optimised structure of the intramolecular PCET for dipole bound anion of glycine nitrile. (B) MP2(CPCM)/aug-cc-pVDZ optimized structure of a similar
intramolecular PCET as shown earlier in for dipole bound anion of cyanohydrine. Color coding of atoms: N : Blue, O: Red C: Greyish Black, H: White. The black arrows show the displacement vector along imaginary mode frequency in transition state. Important interatomic distances are indicated in Å

The fact revealed by our computations that 13 undergoes reduction in contrast to 12 which experiences a kinetic roadblock, which is in full agreement with the experimental findings of Sutherland et al.\cite{15} 15 undergoes a PCET reaction leading to the formation of 16. 16 happens to be a radical anionic species characterized by its E conformation (see Figure 11 and Figure 12). 16 transforms via a cis-trans isomerization to form the corresponding Z isomer, 17 via TS₁₆-₁₇ (see Figure 11 and Figure 12). The free energy barrier for this cis-trans isomerization turns out to be 22.9 kcal/mol at MP2(CPCM)/aug-cc-pVDZ (24.5 kcal/mol at MP2(CPCM)/aug-cc-pVTZ/MP2(CPCM)/aug-cc-pVDZ) level of theory. We realized that two units of 17 can come together and undergo the unique PCET (as discussed earlier for the valence bound anions of 1). However, our repeated attempts to optimize the dianionic intermediate 18 invariably converged to the structure of TS₁₈-₁₉ involved for the PCET step. One of the plausible reasons for this issue could be the flatness of the potential energy surface in the locality of TS₁₈-₁₉ and 18. As observed in the previous case 1 the dianionic intermediate and analogous TS are practically isoenergetic and hence implying the flatness of potential energy surface. The occurrence of PCET leads to the formation of the reduction products 13 and the imine, 19.
The results presented in this chapter thoroughly emphasize the role of dipole bound anions in prebiotic chemical reactions. Interestingly, the unraveled mechanistic protocol avoids the formation of reactive neutral free radical species like H$_2$C=N$^•$, which causes radical proliferation, and ultimately disturbing product selectivity.

So the necessity of chemical selectivity requires that molecular radical anion based mechanistic pathways to be more likely to be operative than any neutral free radical chain reactions in the prebiotic context, which firmly establish in this chapter.

Figure 13. Steps for reduction of nitrile bond of HCN and PCET to form H$_2$C=NH and HCHO subsequently forming glycine nitrile and cyanohydrins. Colour coding of atoms of optimized geometries - H: White, C: Grey, N: Blue, O: Red
Figure 14. The free energy profile in kcal/mol for the reduction of cyanohydrins after electron attachment at the MP2(CPCM)/aug-cc-pVDZ. Colour coding of atoms: N: Blue, O: Red, C: Greyish Black, H: White. The black arrows show the displacement vector along imaginary mode frequency in transition state.

5.3 Conclusion

The study by Sutherland and co-workers established that photo-irradiation of a Cu based photo redox reagents in an aqueous solution of HCN led to the formation of “solvated electrons” which in turn facilitated the production of sugar precursors. The theoretical investigations reported in this chapter establish the mechanistic details of
formation of these sugar precursors via a photoredox reaction in an aqueous HCN solution. The theoretical findings further ascertain the nature of “solvated electrons”, which are produced in the aqueous medium from the photoredox reagent in the form of dipole bound anions. We also report here the first instance of two solvated dipole bound anions, [HCN](-) with doublet spins associating to form a singlet dianionic entity in the aqueous phase. The driving force behind the association was found to be the aromatic stabilization gained upon the formation of the dianionic cyclic six membered entity. The six membered aromatic intermediate underwent an unique proton coupled electron transfer facilitating the reduction of the nitrile bond and thereby producing [HCNH](-) and CN(-). The formed [HCNH](-) molecular anion naturally abstracts a proton from the solvating water molecule thus producing OH(-) and H2C=NH (an imine). The hydrolysis of imine are well known in acidic environment and leads to the formation of formaldehyde. Alternatively the imine upon nucleophilic addition of CN- anion formed glycine nitrile. Formaldehyde also in presence of CN(-) undergo nucleophilic addition and forms cyanohydrins. Our theoretical investigations presented in the chapter additionally revealed the detailed reasons for preferential reduction of cyanohydrin over glycine nitrile in presence of solvated electrons. The interesting aspect of the proposed mechanism is that the kinetic and high thermodynamic favorability of the dianion formation impedes the possibility of formation other reactive free neutral radical species like OH- which if formed would have destroyed the chemical selectivity of the process.

5.4 Computational Details.

5.3.1 Static Quantum Chemical Computations
The ORCA program package was used to carry out the NEVPT2\textsuperscript{[35],[36]} within the COSMO solvent model\textsuperscript{[37,38]} with water as solvent. The single point N-electron Valence Perturbation theory (NEVPT2) computations were performed on MP2 optimized \([\text{Cu(CN)}_3]^2(-)\) geometry.LANL2DZ basis set for valence electrons was used along with LANL2 pseudo-potential, for core electron, for the Cu centre in addition to correlation consistent Dunning’s double zeta aug-cc-pVDZ basis set for C and N atoms was used in NEVPT2 computations. This basis set combination has been denoted as B1. A state averaged CASSCF calculation has been done to compute the excitation energy of the \([\text{Cu(CN)}_3]^{2(-)}\) complex, within the COSMO solvent model with water as solvent, for equal weight for the two electronic states involved in the excitation process with a 4 electron in 4 active orbital CAS (4,4) and then using the multi-configurational wave function a state averaged NEVPT2 calculation for those two states was performed. The optimization of transition states and intermediates were carried out at the B3LYP and MP2 level of theory and taking the polar continuum solvent model (CPCM)\textsuperscript{[39]} and water as solvent, to account for solvent effects, in conjunction with aug-cc-pVDZ basis sets for all reaction pathways investigated except for the \([\text{HCN}]^{(-)}\) dipole bound anion formation from the organometallic complex, i.e. the reaction sequence 4 to 6 shown in Figure 1. For further accuracy optimizations were conducted with augmented triple zeta quality basis sets, aug-cc-pVTZ for the structures and energies for all reactions with \([\text{HCN}]^{(-)}\) (reaction sequences shown in Figures 3-5). For the rest of the reactions as shown in Figures 8-10 we did only single point computations at MP2(CPCM)/aug-cc-pVTZ level of theory at MP2(CPCM)/aug-cc-pVDZ optimized geometries. The maximum deviation for the computed total energies and free energies between the
two different basis sets used was found to be less than 1.5 kcal/mol. For reaction sequence 4 to 6 the molecular geometries were optimized at B3LYP and MP2 level of theory in gas phase followed by single point solvent phase computation for total energies at MP2 within the CPCM approximation using LANL2DZ basis set for valence electron with LANL2 pseudopotential for core electrons of Cu and aug-cc-pVDZ basis sets for C, N, H and O atoms. Gaussian 09 quantum chemistry suite\cite{40} was used for the optimizations and computations of harmonic frequencies of transition states and intermediates.

5.3.2 Molecular Dynamics Studies:

Initially, 58 water molecules, using packmol package,\cite{37} were taken in the cubic box of size 12.020 × 12.020 × 12.020 Å$^3$ to maintain the density 1 kg-m$^{-3}$ and equilibrated for 6.9 ps using PBE functional.\cite{41(a)} One water molecule was then replaced with MP2 optimized structure of the dianionic intermediate. The simulation was conducted at 300 K and Nosé Hoover chain thermostat \cite{41(b)} was employed to create canonical ensemble. A fictitious mass of 700 au was used for the electronic orbital degrees of freedom and a time step of 0.096 fs was used for the integration of equations of motion. The system was defined using the Kohn-Sham density functional theory with plane wave basis set and the core electrons were treated with the ultra-soft pseudo-potential.\cite{41(c)} A plane wave cut off of 30Ry was used. An additional simulation was also performed without adding two protons to the system. The time step of 0.144 fs was used for the integration of equations of motion. The other details are same as previous simulation.
References


[34] See Computational Details for additional details and discussion.


[40] Gaussian 09, Revision A.02, 2009, Frisch et al. Full citation in SI.