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Prebiotic Synthesis of Glycolaldehyde and Glyceraldehyde from Formaldehyde: A Computational Study on the Initial Steps of the Formose Reaction

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In this work, the initial steps of the mechanism of the Formose reaction (FR) is computationally studied using DFT methods. The FR has been considered to be a relevant process in the prebiotic evolution leading to several types of sugars or carbohydrates. These molecules are some of the basic building blocks of the life. The dimerization of formaldehyde was found to take place *via* an intramolecular deprotonation reaction, leading to the formation of an intermediate which, after an isomerization, forms a Ca-complex of the *cis*-enediol tautomer of glycolaldehyde. The aldol reaction of this complex with additional formaldehyde gave glyceraldehyde, the simplest aldotriose. The catalyst $Ca(OH)_2$ plays a dual role in the reaction, acting as a base (in the intramolecular deprotonation) and as Lewis acid (activating the carbonyl group) in the aldol addition.

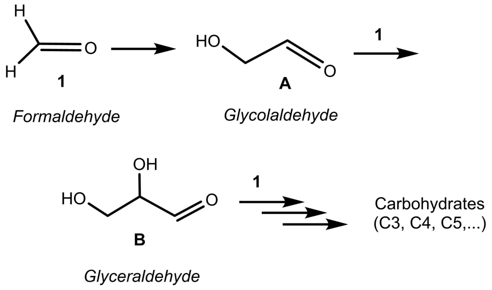
Introduction

The scientific study of the origin of the life is a very interesting but a very challenging problem, especially when considered from the standpoint of the chemistry.[1,2,3]

As the study of the origins of life approaches the times of the *Haddean Eon*,[4] the research is faced with the question of the prebiotic origins of the main classes of biomolecules (sugars, lipids, amino acids),[5] and the dynamics of compositional landscape.[6]

In this work, we computationally explore the prebiotic formation of sugars, which are very important molecules in many biological structures and processes.[7]

It has been proposed that a quite plausible synthetic route for the prebiotic formation of different types of sugars (aldoses and ketoses) is the so called, *"Formose Reaction"* (*FR*).[8,9] The *FR* was discovered in 1861 by Butlerov, who observed that formaldehyde **1** (Scheme 1) when placed in an aqueous basic medium (*e.g.*, with an aqueous solution of calcium hydroxyde), gave rise to a complex mixture of sugar-like organic compounds.[10]



Scheme 1. Prebiotic formation of sugars *via* the Formose Reaction (*FR*).

Primordial formaldehyde (the simplest aldehyde), which, according to Cleeves[11] was a component of the prebiotic atmosphere of Earth, could be converted in different kinds of sugars.[12] *FR* is not actually a single reaction, but a set of processes, involving different types of reactions (as aldol reactions and isomerizations). As shown by Robinson, Huck and co-workers, in an study of a model *FR*, the products distribution respond to the fluctuations in the environment.[6]

According to the proposal of Appayee and Breslow (summarized in Scheme 2),[9c] the initial slow dimerization of **1**, leading to glycolaldehyde **A**, a two carbon-containing intermediate, is followed by an aldol reaction of **1** (which is present in excess in the reaction medium) with intermediate **A** (the *cis*-enediol tautomer form). This aldol condensation reaction leads to the simplest aldotriose, glyceraldehyde **B**. It has been proposed that in these reactions, the different carbonyl compounds involved are forming cyclic Ca^{2+} complexes, through the corresponding *cis*-enediol tautomers.[9c] In the subsequent aldol reactions, a formal incorporation of a *"CH_2OH"* fragment, takes place. In these set of reactions other sugars (tetroses -**D**, **E**, pentoses, and higher carbohydrates) are formed.

Regarding the importance of the *FR* in the prebiotic origin of biologically important sugars, a relevant point, the availability

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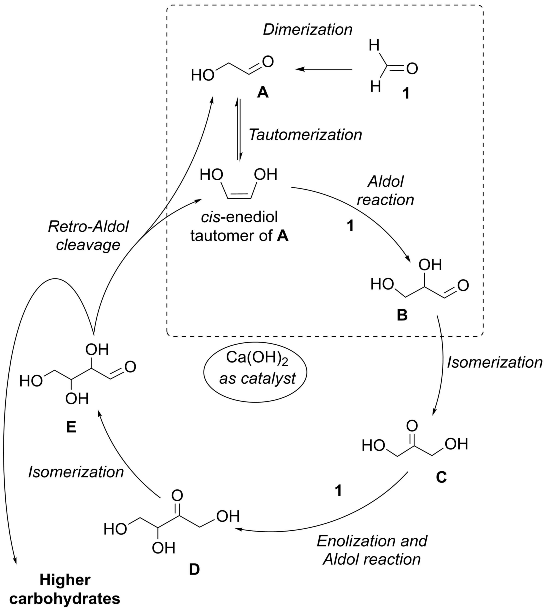


Scheme 2. General course and some relevant intermediates of the Ca(OH)2-catalyzed Formose reaction, as proposed by Appayee and Breslow (ref. [9c]). The reactions studied in this work are those shown inside the frame.

of formaldehyde, is to be addressed. As Cleeves has pointed out,[11] there are several possible sources and sinks for the prebiotic formaldehyde, but that the concentration of formaldehyde in the primitive seas appears to be too much dilute for the *FR* to take place. In addition, it has been argued that in the alkaline conditions prevailing in the *Hadean Eon*, several side-reactions will cause a significant decrease of the concentration of formaldehyde available for the *FR*.[13]

However, according to an experimental study by Kawai et al.[14] a mineral reservoir for formaldehyde could originates in the reaction of sulphur dioxide of volcanic origin with **1**. This well-known reaction[15] involves the addition of bisulfite anion (formed in the reaction of SO_2 with H_2O) to the carbonyl group of formaldehyde. This reaction is reversible, and the bisulfite addition compound formed could easily revert to **1** and sulphur dioxide, making the formaldehyde available for the *FR* and largely avoiding the Cannizzaro disproportionation and other possible side reactions.

Several theoretical studies have been carried out on the *FR* and related processes. Thus, Tajima and co-workers,[16] have reported a semiempirical study of the mechanism of the FR catalyzed by a thiazolium salt. Using DFT methods, Kua *et al.*, studied the kinetics and thermodynamics of the oligomerization of formaldehyde in neutral water, including the formation of glycolaldehyde.[17]

Eckhardt and co-workers, based on the results of pyrolysis experiments and computational studies, have proposed that in non-aqueous conditions (a scenario close to extraterrestrial environments or interstellar clouds), the very reactive intermediate, hydroxymethylene, a formaldehyde-derived nucleophilic carbene, could participate in fast, almost barrierless, reactions, leading to glycolaldehye and glyceraldehyde intermediates.[18]

On the other hand, Jeilani and Nguyen, in the context of studies regarding the formation of RNA nucleosides, have described a free-radical reaction pathway for the formation of intermediates as glycolaldehye and glyceraldehyde, in which Ca^{2+} cations are involved.[19]

Due to the relevance of *FR*[20] in order to explain the abiotic origin of sugars of biological interest we considered that the theoretical studies of several reaction mechanisms of this process, could be of interest, especially in the case of dimerization of formaldehyde, that according to Appayee and Breslow[9c] is the slowest step of the reaction and follows an undetermined mechanism. In this regard we carried out a DFT computational study, at the M062X/Def2QZVP level of theory (see the Computational Methodology section for details) of the initial steps of this process, considered to follow an ionic mechanism.

Results and Discussion

According to Lane and co-workers,[21] life could have appeared in alkaline hydrothermal vents, so we considered that a minimal model for the FR should include Formaldehyde and calcium hydroxyde, which has been reported[9c,6] to catalyze the *FR*.

In this theoretical study of the mechanism of the FR, we focus on three reactions: the formation of the critical intermediate glycolaldehyde (**A**, Scheme 2) by a dimerization reaction of **1**, its isomerization to give the corresponding *cis*-enediol tautomer intermediate, and the aldol reaction of this tautomer with **1** to form the simplest aldotriose, glyceraldehyde **B**. The ionic mechanisms for the reactions indicated were explored, even though that depending on the reaction conditions, different mechanistic routes could be followed.

In the extraterrestrial environments, or in the presence of strong sources of UV radiation (as in the cases when electric sparks were used to simulate atmospheric lightnings), the operation of photochemical or radical mechanisms have been previously proposed.[22] Thus, for example, the formation of intermediate **A** could involve a photochemical or a radical mechanism.[18] Also, the related pinacol synthesis and acyloin ester condensation are considered to take place through a radical mechanism.[22c]

On the other hand, under the typical conditions of the *FR*, as described by van Duppen et al.,[6] Kim et al.,[9b] Appayee and Breslow,[9c] and Sojo and co-workers,[21] ionic mechanisms will probably be involved.

The FR is usually carried out in alkaline conditions at moderate temperatures.[10b,21] Also, it has been pointed out by Benner and co-workers, that Ca^{2+} ion appears to be an essential ingredient in the first step of FR.[9b] Accordingly, we have studied possible ionic mechanisms for the dimerization of **1**, in presence of a base, modeling the catalyst[23] as $Ca(OH)_2$. This catalyst could be in the un-dissociated form; on the other hand the Ca^{2+} cation could be coordinated to water molecules and to hydroxy anions, depending on the exact conditions, these different species being in chemical equilibrium.

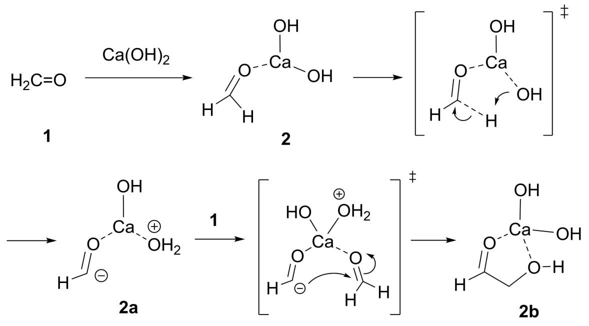
In this regard, we decided to choose the un-dissociated form of $Ca(OH)_2$. as a more general model for the catalyst.

Base-catalyzed dimerization of formaldehyde: formation of glycolaldehyde A

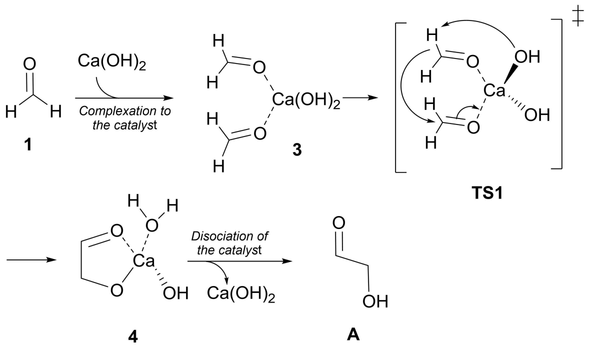
The critical intermediate glycolaldehyde **A** originates from the dimerization of formaldehyde **1** (Scheme 1). As this reaction involves the coupling of two electrophilic carbon atoms, it is expected to have a high activation barrier. Actually, in the study carried out by Appayee and Breslow,[9c] the dimerization of **1** is mentioned to be a quite slow reaction.

The simplest possibility for an ionic dimerization of **1** involves the mechanism shown in Scheme 3: (*i*) the formation of the binary calcium complex **2**, between **1** and $Ca(OH)_2$, (*ii*) the intramolecular deprotonation of formaldehyde to form the zwitterionic complex **2a**, and (*iii*) the nucleophilic addition of **2a** to a second molecule of **1**.

The stationary points for complexes **2** and **2a** were found on the corresponding potential-energy surface (PES), but, despite an extensive search, it was not possible to locate a transition state accounting for the formation of **2b** by addition of zwitterionic complex **2a** to **1** and, accordingly, the stepwise mechanism was discarded.



Scheme 3. A possible stepwise mechanism for the ionic dimerization of formaldehyde.



Scheme 4. $Ca(OH)_2$-catalyzed dimerization of formaldehyde **1** to form intermediate **4**, a calcium complex of glycolaldehyde. The catalyst regenerates by dissociation of complex **4** into $Ca(OH)_2$ and free **A**.

Next, it was explored the PES corresponding to a concerted dimerization of **1** in the presence of calcium hydroxide, as shown in Scheme 4.

The main geometrical parameters of the stationary points located for this reaction mechanism are shown in Figures 1 and 2. The coordination complex **3** (Figure 1) shows a distorted tetrahedral geometry and the formaldehyde coordination is reflected on the increase, from 1.194 Å to 1.208 Å, of the carbon-oxygen bond length of the formaldehyde fragment.

According to the calculations carried out, the formation of the coordination complex **3** is a barrierless process, this complex being predicted to be 13.9 kcal mol^{-1} more stable than the reactants.

The dimerization of formaldehyde was found to take place *via* an intramolecular reaction through the transition state **TS1**, leading to the formation of intermediate **4** (Figure 2).

The imaginary normal mode of **TS1** ($-150.9\ cm^{-1}$) corresponds to the removal of one of the formyl hydrogens and to a C–C bond formation. The analysis of the intrinsic reaction coordinate (IRC) indicates that the formation of **4**, by dimerization of **1**, is a concerted reaction even if very asynchronous: the intramolecular deprotonation, involving one of the hydroxy groups of the catalyst, takes place first on the reaction

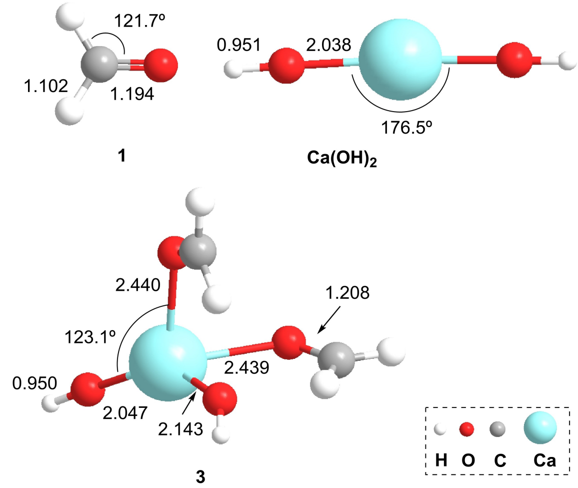


Figure 1. Selected geometrical parameters of reactants (formaldehyde **1** and calcium hydroxide), and the coordination complex, **3**. Bond lengths in Å, angles in degrees).

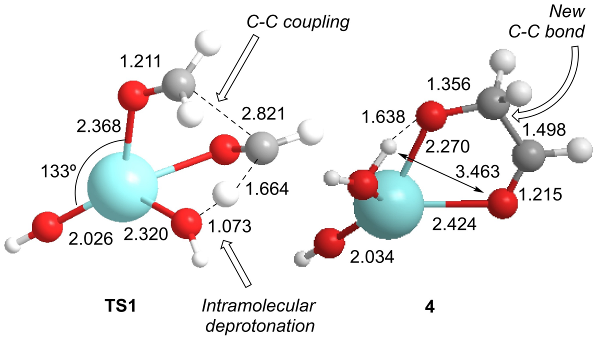


Figure 2. Stationary points corresponding to **TS1** and intermediate **4** (bond lengths in Å, angles in degrees).

coordinate being followed by the formation of the bond between the carbon atoms of the two molecules of formaldehyde.

The catalyst $Ca(OH)_2$ plays a dual role in the reaction, acting as a base (in the intramolecular deprotonation) and as Lewis acid (activating the carbonyl group of one of the formaldehyde molecules towards a nucleophilic addition).

The stationary point **4** corresponds to the product of formaldehyde dimerization and has the structure of a Ca^{2+} complex of the di-alkoxide-derived from **A**, with a hydrogen of the hydroxyl group of glycolaldehyde **A** transferred to a water molecule, which is also coordinated to the calcium cation.

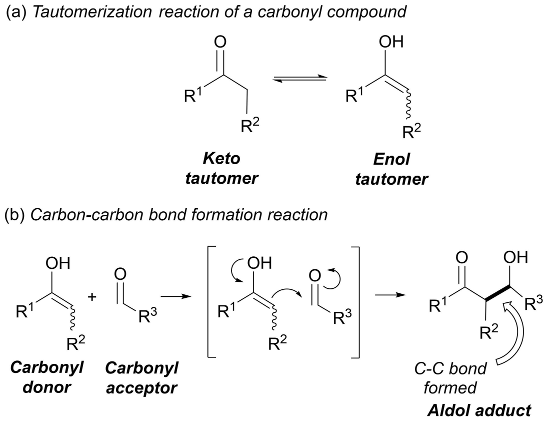
According to these calculations, the value of the activation barrier for the dimerization of formaldehyde, is predicted to be $\Delta G^{\#} = +21.9\ \mathrm{kcal\,mol^{-1}}$. The free glycolaldehyde **A**, detected in the FR, could be produced when complex **4** dissociates and the free catalyst (*e.g.*, calcium hydroxide) is re-generated (see Scheme 4).

An alternative version of this mechanism, involving two molecules of the catalyst was also considered, but the predicted activation free-energy was significantly higher than the value found for the mechanistic pathway depicted in Scheme 4, so this alternative mechanism was discarded.

Catalyzed aldol reactions of glycolaldehyde with formaldehyde: formation of glyceraldehyde B

The different carbohydrates produced in the FR[9,10] are formed by the elongation of the carbon chain, starting with the two carbon-containing intermediate **A**: the aldol reaction of **1** with **A**, leads to glyceraldehyde **B**. Subsequent additions of formaldehyde (followed by the corresponding keto-enol tautomerizations of the intermediates formed) gave rise to a more complex carbohydrate (see Scheme 2).[17]

According to the currently accepted mechanism, an aldol reaction starts with the formation an enol tautomer of one of the carbonyl compounds (*carbonyl "donor"*, scheme 5a).



Scheme 5. General mechanism for the aldol reactions of carbonylic compounds.

This intermediate undergoes a nucleophilic addition towards a carbonyl group (*carbonyl "acceptor"*), leading to the formation of a new C–C bond (Scheme 5b).

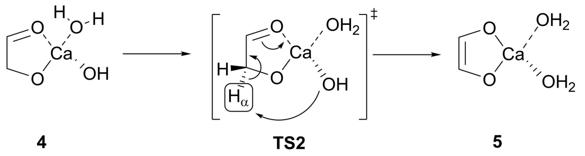
In the current case, intermediate **4** (which is formed in the dimerization reaction of formaldehyde shown in Figure 2), could undergo an intramolecular tautomerization, *via* the transition structure **TS2**: an hydroxyl group of the catalyst, removes a hydrogen atom at the α position of the carbonyl bond in **4**, leading to the reaction product **5**, the enol tautomer of **4** (see Scheme 6).

The stationary points located for the intramolecular isomerization of complex **4** to form intermediate **5**, through transition state **TS2**, are shown in Figure 3.

The imaginary frequency of **TS2** ($-1142.2\ \mathrm{cm^{-1}}$) corresponds to the α-hydrogen removal by the hydroxyl group bonded to calcium atom and to the concerted formation of a C–C double bond. The formation of intermediate **5** from **4**, causes a C–C bond length shortening and a light increase of the C–O bond length. As can be seen in Figure 3, the structure of **5**, corresponds to a coordination complex of Ca^{2+} cation and the alkoxide of *cis*-enediol tautomer of glycolaldehyde and two water molecules. The activation barrier for the isomerization of intermediate **4**, to give the Ca^{2+}-complex **5**, is predicted to be $\Delta G^{\#} = +28.2\ \mathrm{kcal\,mol^{-1}}$.

The catalyzed aldol reactions usually require the formation of a metallic enolate (as shown in Scheme 7).

In these reactions, a Lewis acid-coordinated carbonyl acceptor, with an increased electrophilicity reacts with the metallic enolate, showing an enhanced nucleophilicity.



Scheme 6. Intramolecular tautomerization of **4** to give the Ca^{2+}-dienolate **5**.

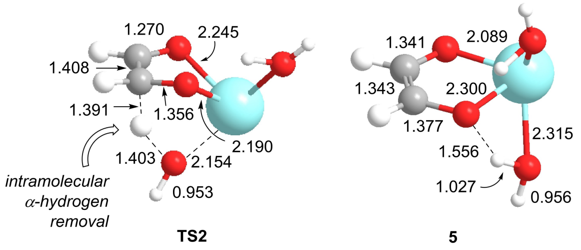
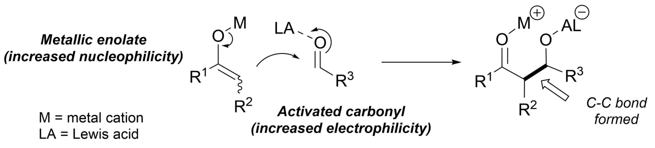


Figure 3. Selected geometrical parameters for **TS2** and complex **5** (bond lengths in Å).



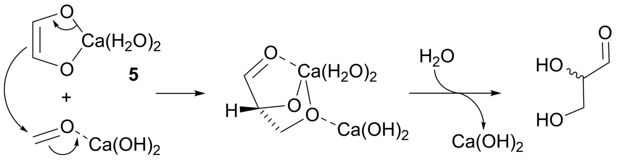
Scheme 7. Mechanism of a catalyzed aldol reaction.

In the *FR*, the aldol reaction leading to glyceraldehyde **B**, involves the addition of intermediate **5**, acting as a nucleophile to the complex **2**, in which the coordination to $Ca(OH)_2$ increases the electrophilicity of formaldehyde (Scheme 8) and gave the calcium complexes **6a** or **6b**.[20]

The aldol reaction of **5** with **2** appears to be barrierless: a detailed exploration of the corresponding PES does not allow to locate a transition state for the formation of product **6a** or **6b**. Both reactants, **2** and **5**, could form different ionic couples of similar energy and depending on which C–C bond is formed in this process, two very stable minima, **6a** or **6b**, are originated (Figure 4).

A transition state, **TS3**, corresponding to the transformation between **6a** and **6b**, was located, and the imaginary frequency ($-23.9\ cm^{-1}$) is associated with a normal mode corresponding to the movement of the carbon atom of activated formaldehyde **2** moiety between the two carbon atoms of aldol adducts **6a** and **6b**. The dissociation of either, complex **6a** or **6b**, leads to the free (*S*)- or (*R*)-glyceraldehyde, respectively.

The full reaction profile for the first three steps of the calcium hydroxide-catalyzed Formose Reaction studied in this work, namely, the dimerization of formaldehyde **1** to give the complex **4**, the isomerization of **4** to give the dienolate **5**, and the aldol reaction of **5** with **2** leading to the calcium complexes **6a** and **6b**, is shown in Figure 5.



2 **6a** (or **6b**) **B**

Scheme 8. Calcium hydroxide catalyzed aldol addition reaction of complex **5** to complex **2** to give the Ca^{2+}-complex of glyceraldehyde **6a**. The hydrolysis of **6a** to give free glyceraldehyde **B** is also shown.

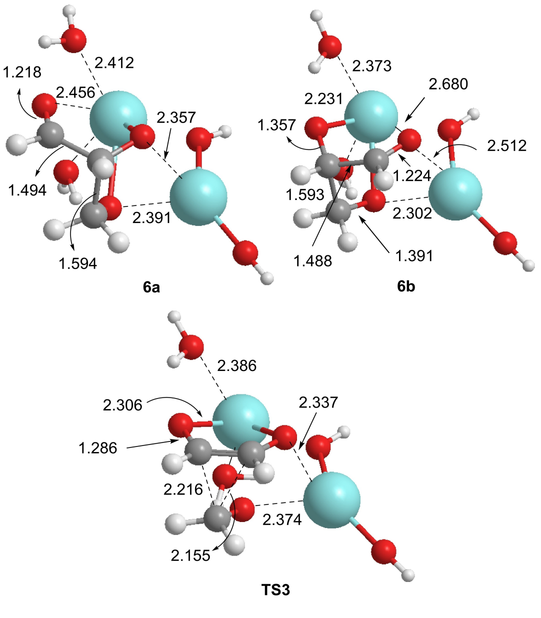


Figure 4. Stationary points (**6a**, **6b** and **TS3**) located for the catalyzed aldol reaction of **5** with **2** (bond lengths in Å).

The effect of the $Ca(OH)_2$ catalysis is so strong that the aldol addition reactions leading to the aldol product (the minima **6a** or **6b**), is a barrierless and very exothermic process. According to the calculations reported in this work, the reaction rate of the $Ca(OH)_2$-catalyzed Formose Reaction is determined by the steps of dimerization of formaldehyde **1** and isomerization of the calcium complex **4**.

The great exothermicity of the aldol addition reaction of dienolate **5** with the Lewis acid-activated formaldehyde **2**, leading to the formation of glyceraldehyde complexes **6a** and **6b**, strongly favors the formation of glycolaldehyde **B**, a critical intermediate in the FR process, in good agreement with the mechanistic proposal by Appayee and Breslow.[9c]

For the sake of comparison, the uncatalyzed aldol reaction of glyceraldehyde **A**, through its tautomer **7** with formaldehyde, was also studied (Scheme 9).

The stationary points located for the uncatalyzed reaction of **7** with **1** are shown Figure 6. In transition state **TS4**, the formation of the bond between a hydrogen atom of **7** and the oxygen of formaldehyde is concerted with the C–C bond formation, to give the intermediate glycolaldehyde, **B**.

According to these calculations, in the case of the uncatalyzed aldol reaction, the activation free-energy of the is predicted to be $\Delta G^{\#} = +19.7\ kcal\,mol^{-1}$. Since the catalyzed aldol reaction is a barrierless process (see Figure 5), it can be

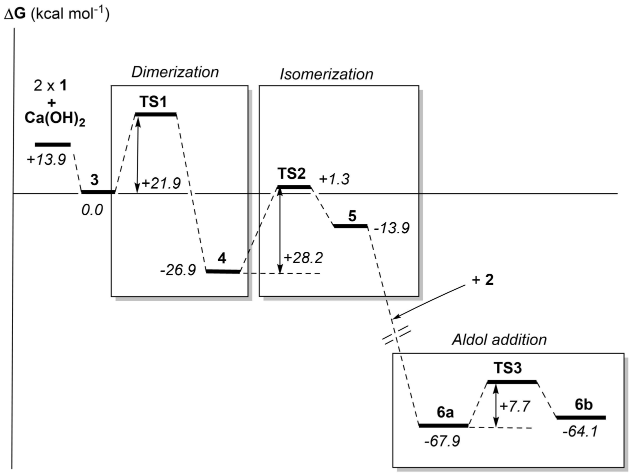
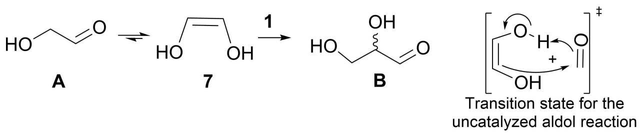


Figure 5. M062X/Def2QZVP reaction profile (not a scale) corresponding to the $Ca(OH)_2$-catalyzed transformation of formaldehyde **1** into the aldol complexes **6a** and **6b**. The Gibbs free energies of aldol products **6a**, **6b** and transition state **TS3** are relative to the ΔG (**5**+**2**).



Scheme 9. Tautomerization of glyceraldehyde **A** to form the cis-enediol **7**, followed by the uncatalyzed aldol addition of **7** to **1**, to give glyceraldehyde **B**.

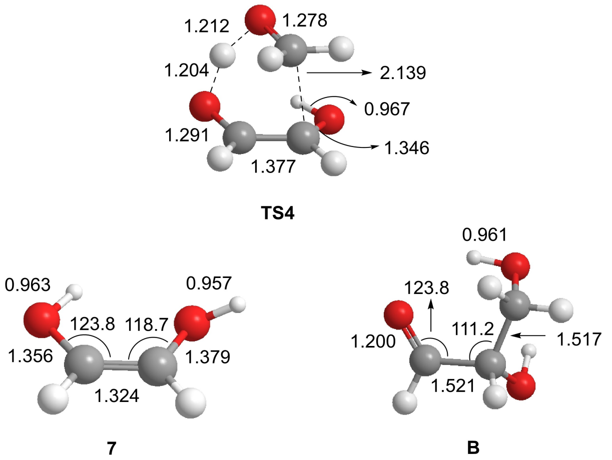


Figure 6. Stationary points for the uncatalyzed aldol reaction of cis-enediol **7** with formaldehyde to give glycoladehyde **B**.

concluded that the presence of Ca(OH)2 clearly accelerates the aldol reaction leading to glyceraldehyde **B**.

Conclusions

The results of a DFT study of the early steps of the Formose reaction (which has been proposed to be the process leading to carbohydrates in pre-biological evolution) are reported. It is shown that in these conditions, calcium hydroxide could catalyze an ionic mechanism for the dimerization of formaldehyde, resulting in the formation of glycoladehyde.

In addition, the catalyzed aldol reactions could lead to the critical intermediate glycolaldehyde. These theoretical results are in good agreement with the previous experimental findings.

Additional work aimed at the study of the formation of the important intermediate 1,3-dihydroxyacetone **C** and the autocatalytic character of the Formose Reaction is underway.

Computational Methodology

The geometry of all the stationary points found in the potential-energy surfaces (PES) of the reactions studied in this work was fully optimized with the functional MO62x, using the Def2QZVP basis set.[24]

Each stationary point was characterized either, to be a minimum or a first-order saddle point (transition state) by computing the harmonic vibrational frequencies at 298.150 K and 1.0 atm. The connection of either the reactants or products with the corresponding transition structure was established by using the intrinsic reaction coordinate (IRC) method.

The calculations described in this work were carried out with the *Gaussian16* suite of programs.[25]

Supporting Information

The cartesian coordinates and energies of the stationary points located are collected in the Supporting Information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: carbohydrates · DFT calculations · formaldehyde · formose reaction · pre-biotic synthesis

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