Formation of the Heyns rearrangement products in dihydroxyacetone and glycine Maillard reaction: A computational study

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Abstract

Density functional theory computations at the standard state on the proposed mechanisms of dihydroxyacetone and glycine Maillard reaction under different pH conditions have revealed that dihydroxyacetone + deprotonated glycine and dihydroxyacetone + unprotonated glycine reactions are more favorable than dihydroxyacetone + protonated glycine and dihydroxyacetone + glycine zwitterion reactions for the formation of the Heyns rearrangement products (HRPs). The gaseous phase reaction is assumed more feasible than the aqueous phase reaction for the production of HRPs. Due to the possibility of the production of both of the enol and keto forms of HRPs, the rate of browning in the dihydroxyacetone + deprotonated glycine reaction is assumed higher than that of the others. Dihydroxyacetone + protonated glycine and dihydroxyacetone + glycine zwitterion reactions are not favorable for the formation of HRPs and, therefore, the reaction is assumed hindered under these conditions and the rate of browning is supposed to be lower than that of the others. Possibilities for the conversion of dihydroxyacetone to glyceraldehyde and formation of hydroxyacetaldehyde from dihydroxyacetone as a C2-fragmentation product have also been evaluated.

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Keywords: Heyns rearrangement products; Dihydroxyacetone; Glycine; Maillard reaction; Density functional calculations.

1. Introduction

Non-enzymatic browning or the Maillard reaction (Maillart, 1912) is one of the most important reactions in controlling food quality and nutritional value. The reaction occurs between carbonyl compounds, especially reducing sugars, and compounds with free amino groups, such as amines, amino acids, and proteins. It occurs on heating or on prolonged storage, and is one of the deteriorative processes that take place in stored foods (Davidek, Velíšek, & Pokorný, 1990; Eskin, 1990; Macrane, Robinson, & Saadler, 1993). The reaction can also take place in the human body, and is therefore important in the medicinal arena (Meade, Miller, & Gennard, 2003; Ledl & Schleicher, 1990; Reber et al., 2002). Although about 90 years have passed since the discovery of the Maillard reaction, and many results have been gathered later on, still there is no potential explanation for its mechanism. Several schemes have been proposed to explain the mechanism of the reaction (Hodge, 1953; Namiki & Hayashi, 1983; Tressl, Nittka, & Kersten, 1995). Of these, the Hodge-scheme (Hodge, 1953) is the most accepted and indicates the very complex nature of the reaction. Due to the complexity of the intermediates and the final products (or melanoidines), controlling the Maillard reaction, with respect
to food quality, nutritional value and medicinal aspects, is still a major challenge. For controlling the reaction, it is necessary that the reaction mechanism is well understood. However, conducting experiments and analyzing the intermediates and final product mixtures for accurate information is complicated. Though a great number of studies have been conducted about the pathways leading to the formation of melanoidines, the mechanism is still obscure and specific pathways, instead of those based on hypothesis, are not available for the formation of Maillard colors, flavors, antioxidants, and so on. Computational chemistry can be applied to such a complex reaction to obtain useful information, helpful to understand and establish proper mechanisms for the reaction. In this paper, mechanisms for the initial stage of dihydroxyacetone and glycine Maillard reaction under different pH conditions are proposed and described, following the Hodge-scheme (Hodge, 1953). During proposing the mechanisms, formation of the Heyns rearrangement products (HRPs) is considered as the possible product of the reaction. The aim of the present study is to perform Density Functional computations to evaluate the possibility of the formation of different compounds in the proposed mechanisms through the estimation of the Gibb’s free energy changes ($\Delta G^\circ$). The total mass balance for different steps of the reaction has been followed during the calculation of $\Delta G^\circ$. To observe the possible internal energy changes, electronic energy changes ($\Delta E^\circ$) for the formation of different compounds in different steps of the reaction have also been calculated by following the total mass balance of the reaction.

1,3-Dihydroxyacetone or dihydroxyacetone (DHA) is the simplest ketose sugar, which can exist in equilibrium with glyceraldehyde (Gald) (Fig. 1) (Harrold, 1991; Holm, 1996; Lozynski, Rusinska-Roszak, & Mack, 1997; Moore, 1962; Thornalley, Wolff, Crabbe, & Stern, 1984; Yaylayan, Majors, & Ismail, 1999). With considerable biological importance, both of these compounds provide the basis of carbohydrate chemistry (Kobayashi, Igarashi, Takahashi, & Higashi, 1976). DHA is used as an intermediate for the production of tanning agents, emulsifiers, plastifiers, alkyl-type resins and X-ray contrast agents (Feige, Ried, & Bachmann, 1996). It has been reported as the active browning ingredient in sunless tanning lotions, and can induce DNA damage, inhibition of lipid accumulation, and blocking of the cell-cycle (Petersen, Wulf, Gniadecki, & Gajkowska, 2004; Stanko & Adibi, 1986). The mechanism of sunless tanning color that develops after dermal application is due to DHA binding to amino acids in the stratum corneum (Kurz, 1994). Genotoxicity and mutagenic effects of DHA have also been reported (Marnett et al., 1985; Mersch-Sundermann, Schneider, Klopman, & Rosencrantz, 1994; Morita, 1991; Pham, DeMarini, & Brockmann, 1980; Yamaguchi, 1982).

On the other hand, glycine (Gly), the simplest amino acid, can be found in four forms (Eskin, 1990; Harrold, 1991; Holm, 1996; Macrane et al., 1993; Shipar, 2004). Unionized or protonated glycine (UGly, $\text{H}_2\text{N}^\circ-\text{CH}_2-\text{CO}_2\text{H}$) becomes the dominant species in the gaseous state, and can exist at a very low concentration in neutral (pH 7) aqueous solution (Harrold, 1991; Holm, 1996). In acidic solution, glycine is completely protonated ($\text{H}_3\text{N}^\circ-\text{CH}_2-\text{CO}_2\text{H}$) and exists as the conjugated acid (Harrold, 1991; Holm, 1996). Hence, under acidic conditions, e.g., pH < 5.5, protonated glycine (PGly) becomes the dominant species. Glycine zwitterion (GlyZ, $\text{H}_3\text{N}^\circ-\text{CH}_2-\text{CO}_2\text{H}^-$) becomes the dominant species at the isoelectric point of glycine ($I = \text{pH} \approx 6$) (Harrold, 1991; Holm, 1996; Macrane et al., 1993). Production of basic amino groups is facilitated by the alkaline medium and, therefore, deprotonated glycine ($\text{DGly}, \text{H}_2\text{N}^\circ-\text{CH}_2-\text{CO}_2\text{H}^-$) becomes the dominant species under basic conditions (pH > 8) (Eskin, 1990).

The reaction between DHA and Gly has not been well studied and, therefore, the mechanism of the reaction is still obscure. However, it can be assumed that the Heyns rearrangement (HR) can take place in the initial or early stage of the reaction, leading to the production of HRPs (Davidek et al., 1990; Eskin, 1990; Macrane et al., 1993; Wrodnigg & Eder, 2001). The initial stage of DHA + UGly reaction (Fig. 2) may involve firstly the protonation of DHA to PDHA. Nucleophilic attack by Gly on the electron deficient carbon atom of the carbonyl group of PDHA may lead to the production of the dihydroxyacetone–glycine addition compound, $\text{CatDG}$ (2-hydroxy-2-protonated glycinol-1,3-dihydroxy-propane), which can produce the dihydroxyacetone–glycine addition compound, $\text{DGadd}$ (2-hydroxy-2-glycino-1,3-dihydroxy-propane), through deprotonation. Elimination of one molecule of water (H$_2$O) from $\text{DGadd}$ can take place, resulting in the production of the Schiff base of the dihydroxyacetone–glycine addition compound, $\text{DGSB}$. Through protonation, $\text{DGSB}$ can produce the cation of the Schiff base, $\text{Cat-DGSB}$, which can form the enol form of the Heyns rearrangement product, $\text{HRPE}$ (2-glycino-1,3-dihydroxy-prop-l-ene), through deprotonation. Through keto-enolic tautomerization (KET), $\text{HRPE}$ can be rearranged to

![Fig. 1. Interconversion of glyceraldehyde (Gald) and dihydroxyacetone (DHA).](image-url)
its more stable keto form, HRPK (2-glycino-3-hydroxy-prop-1-al).

Production of CatDG in the DHA + PGly reaction (Fig. 2) may occur through the direct nucleophlic addition of DHA and PGly, instead of the formation of PDHA. Consequently, HRPE and HRPK can be formed from CatDG through the mechanism proposed for the DHA + UGly reaction (Fig. 2).

In the initial stage of the DHA + DGly reaction (Fig. 3), nucleophilic addition of DHA and DGly may lead first to the formation of the ionic addition adduct, CatDG(DGly), which can form the dihydroxyacetone–deprotonated glycine addition compound, DGadd(DGly) [2-hydroxy-2-deprotonated glycino-1,3-dihydroxy-propane], through intramolecular rearrangement (IMR). The Schiff base, DGSB(DGly), can be formed through the elimination of one molecule of H₂O from DGadd(DGly), and protonation of DGSB(DGly) can lead to the production of Cat-DGSB(DGly). Deprotonation of Cat-DGSB(DGly) can produce the enol form of the Heyns rearrangement product, HRPE(DGly) [2-deprotonated glycino-1,3-dihydroxy-prop-1-ene]. Through KET, HRPE(DGly) can be rearranged to its keto form, HRPK(DGly).

In the initial stage of the DHA + GlyZ reaction (Fig. 3), nucleophilic addition of DHA and GlyZ may produce firstly the ionic addition adduct, CatDG(GlyZ), which can lead to the formation of the addition
compound, DGadd(DGly), through deprotonation. Subsequent production of HRPE(DGly) and HRPK(DGly) from DGadd(DGly) can occur through the mechanism proposed for the DHA + DGly reaction (Fig. 3). Information regarding DHA + DGly Maillard reaction under different pH conditions is still not available. Previous studies were related mainly to the role of unprotonated amino groups in the Maillard reaction, and generally overlooked the function of protonated, deprotonated amino groups, and amino groups at the isoelectric points. The present study will be helpful to evaluate the role of different Gly species (UGly, PGly, DGly and GlyZ) in the Maillard reaction under different pH conditions involving DHA. Experimental evaluation of the role of these complex species in the Maillard reaction is quite complicated and, therefore, computational methods are used.

2. Methodology

All compounds in the proposed mechanisms (Figs. 2 and 3) have been studied in their gaseous and aqueous phases at the standard state. DHA and Gly can have many conformations in both of the gaseous and aqueous phases (Csaszar, 1992; Hu, Shen, & Schaefer, 1993; Jensen & Gordon, 1991; Kobayashi & Takahashi, 1979; Lejli, Adamo, & Barone, 1994; Lozynski et al., 1997; Palla, Petrongolo, & Tomasi, 1980; Ramek, Cheng, Frey, Newton, & Schäfer, 1991; Wagen et al., 1994; Yaylayan et al., 1999). It is not possible to consider all of these conformations during the calculation of energy changes for different steps in a reaction, especially when it is a complex one, such as the Maillard reaction. Therefore, general optimized structures of DHA and Gly (Figs. 4 and 5) at a specific method (RB3LYP) (Becke, 1992a, 1992b, 1993, 1996; Frisch & Foresman, 1996; Frisch & Foresman, 1998; Hehre et al., 1986; Larid, Ross, & Ziegler, 1996; Miertus & Tomasi, 1982; Miertus, Scrocco, & Tomasi, 1981; Salarub et al., 1991; Springborg, 1995; Young, 2001). 6-31G(d) polarized basis set (Foresman & Frisch, 1996; Frisch & Foresman, 1998; Hehre et al., 1986; Young, 2001) has been used for all calculations. During the optimization, all structural parameters, e.g., bond-lengths, bond-angles and dihedral angles, have been used as variables. The term “Stationary point found” has been verified in the geometry output to confirm the ground state (Foresman & Frisch, 1996; Frisch & Foresman, 1998). Many of the compounds in the proposed mechanisms may be favorable in their cyclic forms (Davidek et al., 1990; Eskin, 1990; Maerane et al., 1993) and, therefore, special care has been taken to avoid the possible intramolecular cyclization during the optimization. All RB3LYP/6-31G(d), PCM/RB3LYP/6-31G(d) or PCM/RHF/6-31G(d) optimized structures have been taken for RB3LYP/6-31G(d) and PCM/RB3LYP/6-31G(d) frequency calculations to achieve the relevant zero point energy (ZPE) and the Gibb’s free energy (G’). Single point energy calculations in the gaseous and aqueous states have been performed on the RB3LYP/6-31G(d), PCM/RB3LYP/6-31G(d) or PCM/ RHF/6-31G(d) optimized structures by using RB3LYP/6-31 G(d) and PCM/RB3LYP/6-31G(d), respectively (Foresman & Frisch, 1996; Frisch & Foresman, 1998). Relevant ZPE have been added to the single point energies to obtain the total electronic energies (E’). Finally, electronic and free energy changes (ΔE’ = E’Product(s) - E’Reactant(s)) and ΔG’ = G’Product(s) - G’Reactant(s), respectively) for different compounds in the proposed mechanisms (Figs. 2 and 3) have been calculated by following the total mass balance of the reaction. Thus, the possibility and internal energy changes for the formation of different compounds in the proposed mechanisms have been investigated.

3. Results and discussion

At a constant temperature and pressure, ΔE and ΔG of a reaction indicate the internal energy changes and spon-


The standard free energies of reaction, respectively. $\Delta G^\circ$ for the formation of different compounds in the proposed mechanisms under different pH conditions (Figs. 2 and 3) are presented in Table 1, and were calculated by using $\text{DHA} + \text{Gly}$ total free energies ($G_{\text{DHA}} + G_{\text{Gly}} - G_{\text{Reactant}}$) as the standard in the equation $\Delta G^\circ = G_{\text{Product}} - G_{\text{Reactant}}$.

![Diagram of reaction pathways]

Fig. 5. RB3LYP/6-31G(d) geometric parameters of unprotonated glycine (UGly), protonated glycine (PGly), deprotonated glycine (DGly) and glycine zwitterion (GlyZ).

Table 1

<table>
<thead>
<tr>
<th>Reactions →</th>
<th>$G_{\text{DHA}} + G_{\text{Gly}}$</th>
<th>$G_{\text{DHA}} + G_{\text{Gly}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[kJ/mol]</td>
<td>[kJ/mol]</td>
</tr>
<tr>
<td></td>
<td>Gaseous</td>
<td>Aqueous</td>
</tr>
<tr>
<td>PDHA</td>
<td>25.1</td>
<td>154.7</td>
</tr>
<tr>
<td>CatDG</td>
<td>$-73.2$</td>
<td>$-32.8$</td>
</tr>
<tr>
<td>DGGd</td>
<td>$-77.5$</td>
<td>$-229.2$</td>
</tr>
<tr>
<td>DGSB</td>
<td>$-173.3$</td>
<td>$-227.3$</td>
</tr>
<tr>
<td>CatDGSB</td>
<td>$-36.0$</td>
<td>$-50.4$</td>
</tr>
<tr>
<td>HRPE</td>
<td>$-74.1$</td>
<td>$-64.4$</td>
</tr>
<tr>
<td>HRPK</td>
<td>$-36.0$</td>
<td>$-82.4$</td>
</tr>
</tbody>
</table>

For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 2 and 3.
Table 2

<table>
<thead>
<tr>
<th>Reactions →</th>
<th>DHA + UGly</th>
<th>DHA + PGly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gaseous</td>
<td>Aqueous</td>
</tr>
<tr>
<td>PDHA</td>
<td>20.1</td>
<td>149.8</td>
</tr>
<tr>
<td>CatDG</td>
<td>–324.6</td>
<td>–67.4</td>
</tr>
<tr>
<td>DGGadd</td>
<td>–71.1</td>
<td>–10.5</td>
</tr>
<tr>
<td>DGSB</td>
<td>–21.9</td>
<td>11.8</td>
</tr>
<tr>
<td>CatDGSB</td>
<td>–263.7</td>
<td>–40.7</td>
</tr>
<tr>
<td>HRPE</td>
<td>–10.8</td>
<td>23.7</td>
</tr>
<tr>
<td>HRPK</td>
<td>–55.6</td>
<td>–24.1</td>
</tr>
<tr>
<td>DHA + DGly</td>
<td>–63.6</td>
<td>–6.8</td>
</tr>
<tr>
<td>CatDG(DGly)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DGGadd(DGly)</td>
<td>–81.3</td>
<td>4.9</td>
</tr>
<tr>
<td>DGSB(DGly)</td>
<td>–57.4</td>
<td>40.8</td>
</tr>
<tr>
<td>CatDGSB(DGly)</td>
<td>–61.2</td>
<td>557.1</td>
</tr>
<tr>
<td>HRPE(DGly)</td>
<td>–83.0</td>
<td>16.6</td>
</tr>
<tr>
<td>HRPK(DGly)</td>
<td>–80.6</td>
<td>–16.4</td>
</tr>
</tbody>
</table>

For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 2 and 3.

\[ \Delta E^e = E^e_{\text{product(s)}} - E^e_{\text{reactant(s)}} \]

The total mass balance of any reaction is important as it is related to the energy changes. The total mass balance of DHA + Gly reaction under different conditions has been maintained during the calculation of \( \Delta G^e \) and \( \Delta E^e \). The main problem in balancing the total mass arises for the protonation (\( \text{+H}^+ \)) and deprotonation (\( \text{-H}^+ \)). Therefore, the following equation has been applied during balancing the total mass:

\[ \text{H}^+ + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ \] (protonation and deprotonation)

According to \( \Delta G^e \) (Table 1), protonation of DHA to PDHA is not favorable in both the gaseous and aqueous state DHA + UGly reactions. It is difficult to explain the unfeasibility of the protonation of DHA to PDHA. According to \( \Delta E^e \) (Table 2) PDHA is electronically more unstable in the aqueous phase than in the gaseous state. In comparison, previous computational study revealed that protonation of Gald is favorable in the gaseous phase Gald + UGly reaction (Shipar, 2004). Except PDHA, formation of all other compounds in the proposed mechanism for DHA + UGly reaction has been found to be feasible in the gaseous state (Table 1). Therefore, it is possible that instead of the protonation of DHA to PDHA, direct nucleophilic addition of DHA and UGly occurs in the gaseous phase Gald + UGly reaction leading to formation of CatDG, which can consequently produce HRPs. It is also possible that some other compounds, such as 1,2,3-10 trihydroxypropane \([\text{H}_2\text{C(OH)}\text{H}_2\text{C(OH)}\text{H}_2\text{C(OH)}]\) formed through the nucleophilic addition of DHA and H$_2$O, are involved in the initial step. Interconversion of DHA to Gald (Fig. 1) is found not to be favorable in both the gaseous and aqueous states. \( \Delta G^e \) and \( \Delta E^e \) for the interconversion of DHA to Gald, have been calculated as 20.5 kJ/mol (relative \( \delta E^e_{\text{gas}} = 20.1 \) kJ/mol) and 1.1 kJ/mol (relative \( \delta E^e_{\text{aq}} = 0.8 \) kJ/mol), obtained by using DHA free energy and electronic energy \( (G^e_{\text{DHA}} \text{ and } E^e_{\text{DHA}}) \) as the standard in the equations \( \Delta G^e = G^e_{\text{Product(s)}} - G^e_{\text{Reactant(s)}} \) and \( \Delta E^e = E^e_{\text{Product(s)}} - E^e_{\text{Reactant(s)}} \), respectively. As DHA is a ketose and Gald is an aldose sugar, and ketoses are naturally more stable than aldoses, interconversion of DHA to Gald is assumed naturally not to be favorable, and the result is consistent with this assumption. The same values for \( \Delta G^e \) and \( \Delta E^e \) with negative signs (\(-20.5, -1.1 \) kJ/mol and \(-20.1, -0.8 \) kJ/mol, respectively) have been found for the interconversion of Gald to DHA, which reveal that interconversion of Gald to DHA is more favorable in the gaseous state reaction than that of the aqueous state, and it is also in agreement with the above natural postulation. However, adequate experimental data are still not available to evaluate this assumption. Some
important geometric parameters of DHA and Gald, used in the present study, are presented in Figs. 4 and 6, respectively.

\[ \text{DHA} + \text{UGly} \] aqueous phase reaction is found not to be favorable for the formation of PDHA, CatDG, DGadd, CatDGSB and HRPE (Table 1). Therefore, it is possible that nucleophilic addition of DHA and UGly immediately follows the elimination of one molecule of \( \text{H}_2\text{O} \) to form DGSB, which will directly rearrange to HRPK through intramolecular rearrangement in the aqueous phase DHA + UGly reaction. It is also possible that some other mechanisms are involved in this case, and sufficient information is still not obtainable. According to \( \Delta E' \) (Table 2), CatDG and CatDGSB have been found electronically to be more stable species than the others in the DHA + UGly gaseous phase reaction, whereas CatDG appears to be a more stable species than the others in the aqueous phase DHA + UGly reaction.

Except CatDG in the gaseous state, formation of all other compounds in the proposed mechanism for DHA + PGly reaction (Fig. 2) has been found not to be favorable in both of the gaseous and aqueous states (Table 1). Therefore, it is assumed that the reaction is hindered for the formation of HRPs under this condition. Some other mechanisms may also be involved in this case. CatDG has been found electronically to be the most stable species in both of the gaseous state DHA + PGly reactions (Table 2).

The Schiff bases (SBs) are one of the most common intermediates in the Maillard reaction (Davidek et al., 1990; Eskin, 1990; Macrane et al., 1993). DHA + PGly and DHA + GlyZ reactions are not favorable for the formation of SBs, whereas, DHA + UGly and DHA + DGly reactions are supposed to be favorable for the formation of SBs, i.e., DGSB and DGSB(DGly), respectively (Table 1). The gaseous phase reaction is assumed more favorable for the formation of SBs (Table 1). DGSB and [DGSB(DGly)] are supposed to electronically be more stable in the gaseous phase DHA + UGly and DHA + DGly reactions, respectively (Table 2). Some important RB3LYP/6-31G(d) optimized geometric parameters of SBs, used in the present study, are presented in Fig. 7.

In both of the gaseous and aqueous states, DHA + DGly reaction has been found as favorable for the formation of all compounds in the proposed mechanism, whereas DHA + GlyZ reaction has been found not to be feasible for the formation of all compounds in the proposed mechanism (Table 1). Therefore, like DHA + PGly reaction, DHA + GlyZ reaction is also postulated to be stalled for the production of HRP(DGly)s in both of the gaseous and aqueous states, and DHA + DGly reaction is assumed to be the most favorable for the production of HRP(DGly)s. In both of the gaseous and aqueous states, DHA + DGly reaction is assumed favorable for the formation of HRP(DGly)s (Table 1), which is in consistent with the previous report for the formation of the Amadori rearrangement products [ARP(DGly)s] in the Gald + DGly reaction (Shipar, 2004). However, production of HRP(DGly)s in the DHA + DGly reaction is assumed to be more favorable than the production of ARP(DGly)s in the Gald + DGly reaction (Shipar, 2004). Formation of HRPK in the DHA + UGly reaction appears to be favorable in both of the gaseous and aqueous states, whereas formation of HRPE is favorable in the gaseous state DHA + UGly reaction (Table 1). In comparison, both of the gaseous and

\[ \text{DGSB} \] and \[ \text{DGSB(DGly)} \] geometric parameters of the Schiff bases.
aqueous phase Gald + UGly reaction were reported as not feasible for the formation of the enol form of the Amadori rearrangement product (ARPE) (Shipar, 2004). Both DHA + PGly and DHA + GlyZ reactions are not favorable for the formation of HRP[HRPE or HRPE(DGly)] and HRP[K or HRPK(DGly)] in both of the gaseous and aqueous states (Table 1) and, therefore, formation of HRP in these conditions is assumed to be impeded. Some other mechanisms may also be involved in these cases. The gaseous phase DHA + Gly reaction is assumed more feasible for the production of HRP than the that of the aqueous phase, which is consistent with the previous report that the gaseous phase Gald + Gly reaction is more plausible for the production of ARPs than that of the aqueous phase (Shipar, 2004).

According to $\Delta E^*$ (Table 2), HRPE is electronically more stable in the DHA + UGly gaseous phase reaction than that of the aqueous phase, whereas it is more stable in DHA + PGly aqueous phase reaction than that of the gaseous phase. HRP[K] has also been found to be electronically more stable in the gaseous phase than the aqueous phase DHA + UGly reaction, and more stable in the gaseous phase DHA + PGly reaction than that of the gaseous phase. It also reveals that HRP[K] is electronically more stable than HRPE in both of the gaseous and aqueous state reactions. HRP[K](DGly) has also been found to be electronically more stable than HRPE(DGly) in both of the gaseous and aqueous phase reactions (Table 2).

HRPs are the primary precursors of melanoidines and, therefore, have great importance in the Maillard reaction involving ketose sugars and amino compounds (Davidek et al., 1990; Eskin, 1990; Macrane et al., 1993; Wrodnigg & Eder, 2001). However, due to comparatively lower stability of these species, isolation and detection of HRP in the Maillard reaction is assumed complicated. HRP[K] possess strong reducing properties (Davidek et al., 1990), and readily undergo further reactions to produce melanoidines through the formation of relative deoxyosones (Davidek et al., 1990; Eskin, 1990; Macrane et al., 1993). HRP[K] have been reported as less reactive than reductones, and about 10 to 100 times more reactive than the parental reducing sugars (Davidek et al., 1990). They crystallize in open chain forms but mainly as $\beta$-pyranoses (Davidek et al., 1990). A number of studies have been reported which show that if sufficient reactants are present and the reaction time is long enough, then ARPs can be formed under physiological conditions (Davidek et al., 1990; Eskin, 1990; Macrane et al., 1993), whereas such reports on HRP[K] are still not available. Some important RB3LYP/6-31G(d) optimized geometric parameters of HRP[K], used in the present study, are presented in Figs. 8 and 9.

Ionic adducts, such as CatDG, CatDGSB, etc., may play an important role during the formation of the melanoidines, especially in DHA + PGly and DHA + GlyZ reactions. As these species are supposed to be formed readily in the reaction, they may have an outstanding role in the production of melanoidines. Direct cleavage or retro-aldolization of these species or other intermediates, HRP[K] as well as the parental sugars, may occur readily during the formation of melanoidines (Davidek et al., 1990; Eskin, 1990; Hodge, 1953; Hollnagel & Kroh, 1998; Macrane et al., 1993; Namiki & Hayashi, 1983; Tressl et al., 1995; Hayashi & Namiki, 1986; Weenen & Tjan, 1994). For example, hydroxyacetaldehyde (Hald) can be formed from DHA by C2-fragmentation.

![Fig. 8. RB3LYP/6-31G(d) geometric parameters of the enol form of the Heyns rearrangement products.](image-url)
ΔG_{gas} and ΔG_{aq} for the production of **Hald** from DHA have been calculated as −0.03 kJ/mol (respective ΔE_{gas} = 12.1 kJ/mol) and −37.6 kJ/mol (respective ΔE_{aq} = −8.9 kJ/mol), respectively. It reveals that formation of **Hald** through the C2-fragmentation of DHA is more favorable in the aqueous state than in the gaseous state. This is consistent with the previous findings that **Hald** is produced as a C2-sugar fragmentation product in the early stage of the Maillard reaction, especially in aqueous solution (Namiki & Hayashi, 1983; Hayashi & Namiki, 1986). Computational studies on **Gald** and Gly Maillard reaction also revealed that formation of **Hald** from **Gald** is favorable in the aqueous state, and not in the gaseous state (Shipar, 2004). Due to the high browning activity, C2-sugar fragmentation products are important in the Maillard reaction. Higher browning activity of **Hald** than other carbonyl compounds has been reported by Namiki and Hayashi (1983), and Hayashi and Namiki (1986). Though **Hald** is not a reducing sugar, having carbonyl and hydroxyl groups it is structurally similar to sugars and, therefore, can lead to the formation of browning products through the Maillard reaction (Davidek et al., 1990; Eskin, 1990; Macrane et al., 1993; Namiki & Hayashi, 1983; Weenen & Tjan, 1994). In **Hald**, the H atoms are electrophilic, and due to the existence of only one hydroxyl group, which is a nucleophile, the electron flow to the carbonyl carbon is assumed lower than that of **Gald**, glucose, etc. Therefore, positive charge on the carbonyl carbon of **Hald** might be higher than that of other carbonyl compounds, and hence, the carbonyl carbon of **Hald** might be more suitable for nucleophilic attack. The nucleophilic amino groups of amino compounds with the loan pair electron on the nitrogen atom can readily attack the electron deficient carbonyl carbon of **Hald**, leading to the formation of melanoidines. For the formation of **Hald** as a C2-sugar fragmentation product, the rate of browning in the sugar–amino compound reaction, such as in DHA + Gly reaction, can be enhanced. By using PClO\textsuperscript{2} semi-empirical quantum-chemical method, some electronic structures of **Hald** have been studied by Fedoronko, TemKovic, Konigstein, Kovacik, and Tvaroska (1980). Peräkyölä (1997) used Ab initio quantum mechanical calculations up to MP4(SDQ)/6-31+G**//**HF/6-31+G*, and the solvent effect has been observed by using the polarisable continuum method (PCM). Some important RB3LYP/6-31G(d) geometric parameters of **Hald**, used in the present study, are presented in Fig. 11.
According to the total mass balance of the DHA + Gly reaction, water plays an important role in the reaction under all conditions. Water is necessary for the initiation of the reaction. One molecule of H_2O in the initial step of the DHA + UGly reaction is necessary for balancing the total mass, whereas two molecules of H_2O for each are needed in the initial step of DHA + PGly, DHA + DGly and DHA + GlyZ reactions. This is in agreement with the earlier findings that water is essential for the Maillard reaction to take place (Ames, 1990; Davidek et al., 1990; Eskin, 1990; Labuza & Saltmarch, 1981; Lea & Hannan, 1949; Macrane et al., 1993; Nursten, 1986). On the other hand, during the formation of HRP, one molecule of H_2O is produced as a by-product in the reaction under all conditions. Hence, finally the reaction under neutral pH conditions (DHA + UGly reaction) contains a total of two molecules of H_2O, and the reaction under other pH conditions (DHA + PGly, DHA + DGly and DHA + GlyZ reactions) contain a total of three molecules of H_2O. This is also in accord to the previous reports that water is a by-product in the Maillard reaction (Davidek et al., 1990; Eskin, 1990; Macrane et al., 1993).

4. Conclusion

Density functional computations have been performed at the standard state on the proposed mechanisms for the Heyns rearrangement during the initial stage of DHA + Gly Maillard reaction under different conditions.
pH conditions. By following the total mass balance, the possibility for forming different compounds in the proposed mechanisms has been investigated through the estimation of $\Delta G^o$ and $\Delta E^o$. The results reveal that basic conditions play an important role during the production of HRP$\_s$. The gaseous phase reaction is assumed more favorable for the production of HRP(DGly)$\_s$ than the aqueous phase reaction. As the production of both HRPE(DGly) and HRPK(DGly) is feasible in DHA + DGly reaction, the rate of browning under this condition is assumed to be higher than that of the others. The Maillard reaction can take place in foods as well as in the human body (human blood is slightly basic) and, therefore, these findings are important and consistent with previous statements (Davidek et al., 1990; Eskin, 1990; Ledl & Schleicher, 1990; Macrane et al., 1993; Meade et al., 2003; Reber et al., 2002).

DHA + UGly reaction under neutral conditions is supposed to be the second most favorable for the production of HRPs, and the reaction in the gaseous state is assumed much more hindered than that of the aqueous state. However, the aqueous phase DHA + UGly reaction has been found not to be feasible for the formation of HRPE. Based on $\Delta G^o$, the possible low energy diagram for the formation of HRPs in DHA + UGly and DHA + DGly reactions are presented in Figs. 12 and 13, respectively. Formation of HRPs in DHA + PGly and DHA + GlyZ reactions is supposed to be unfeasible and, therefore, the rate of browning under these conditions is assumed to be much more hindered than that of DHA + UGly and DHA + DGly reactions. This is in agreement with the previous statement that acidic or protonated forms of amino groups of amino compounds are not favorable for the Maillard reaction (Davidek et al., 1990; Eskin, 1990; Macrane et al., 1993). However, some other mechanisms may be engaged under these conditions. Interconversion of DHA to Hald from DHA is supposed to be more favorable in the aqueous state than in the gaseous state. Adequate information on the DHA + Gly reaction is still lacking and, therefore, to establish a proper reaction mechanism and find out the role of DHA and Gly in vivo as well as vitro, further extensive theoretical and experimental studies on the reaction are still in demand. In addition, the global minima, maxima and transition states of different compounds on the potential energy surfaces are also necessary. In order to fulfill this intention, the theoretical results, presented in this paper, are thought to be helpful for further theoretical investigations. Computational studies on the intermediate and final stages of the reaction are also necessary. The collective result could provide important clues that will be helpful for establishing a mechanism leading to appropriate ways of controlling the Maillard reaction in vivo as well as vitro.

References


