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Formation of pyrazines in dihydroxyacetone and glycine Maillard reaction: A computational study

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Abstract

Based on the electronic and Gibb's free energy changes, the possibility of the formation of 2,5-dimethyl pyrazine (**25Pz**) as one of the probable final products in dihydroxyacetone (**DHA**) and glycine Maillard reaction under different pH conditions is described. Mechanisms for the reaction have been proposed following the Hodge-scheme. Density functional computational calculations at the standard state have been performed on the proposed mechanisms of the reaction. Electronic and Gibb's free energy changes for the formation of different compounds have been estimated by following the total mass balance for different steps of the reaction. The possible order of feasibility for the production of **25Pz** has been found as **DHA** + deprotonated glycine (**DGly**) gaseous > **DHA** + **DGly** aqueous > **DHA** + unprotonated glycine (**UGly**) gaseous > **DHA** + glycine zwitterion (**GlyZ**) gaseous > **DHA** + **UGly** aqueous > **DHA** + **GlyZ** aqueous > **DHA** + protonated glycine (**PGly**) aqueous > **DHA** + **PGly** gaseous phase reactions. Amino-acetone has been found to be the most likely precursor of the pyrazine ring. Oxidation plays an important role during the production of **25Pz**. Water has been found as a by-product during the formation of **25Pz**.

Keywords: 2,5-Dimethyl pyrazine; Dihydroxyacetone; Glycine; Maillard reaction; Density functional computation

1. Introduction

Nonenzymatic browning or the Maillard reaction (Maillard, 1912) is a complex series of chemical reactions, and has received intense interest due to its important role in vivo as well as in vitro (Davídek, Velíšek, & Pokorný, 1990; Eskin, 1990; Ledl & Schleicher, 1990; Macrane, Robinson, & Saadler, 1993; Meade, Miller, & Gerrard, 2003; Odani et al., 1998; Reber et al., 2002; Uchida et al., 1997). Pyrazines (**Pz**s) can be formed as possible flavor compounds through the Maillard reaction during processing of foods (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). They generally contain nutty and roasted aromas, and have been recognized as important flavor components of a large number of cooked, roasted and toasted foods (Ho, 1996). Non-mutagenic characteristics of alkyl pyrazines have been reported, and these unique and sensory properties are important for food industries (Davídek et al., 1990; Wilen, 1970; Wong & Shibamoto, 1996). Production of these compounds is also related to the formation or development of colors (Wong & Shibamoto, 1996). The color of L-rhamnose and ammonia reaction mixture has been reported to become darker as the reaction progress, and as the amount of pyrazine products increases, the color of the mixture changes from colorless to yellow, then brown, and finally dark brown (Shibamoto & Bernhard, 1978). Similarly, it may have affects on the formation of other Maillard products, such as antioxidants, toxicants, etc. However, mechanisms for the formation of Maillard flavors and aromas have not been well studied or well established, and very little information about **Pz**s is available (Akiyama et al., 2003;

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Davídek et al., 1990; Eskin, 1990; Ho & Chen, 1999; Macrane et al., 1993; Shu, 1999; Wilen, 1970). Due to greater complexities, conducting experiments and analyzing the intermediates and final product mixtures for accurate information about the reaction and mechanism for the formation of Maillard flavors and aromas, is complicated. Though a great number of studies have been conducted about the pathways leading to the formation of final Maillard products, the mechanism is still obscure and specific pathways, instead of some hypothesis, are still not available for the formation of Maillard flavors and aromas. Computational model chemistry can be applied on such a complex reaction to obtain useful information, which will be helpful to propose a mechanism to understand the formation of flavors and aromas through the Maillard reaction. Previous density functional computational studies at the standard state on glyceraldehyde (**Gald**) and glycine (**Gly**) Maillard reaction have revealed that **Gald** + deprotonated glycine (**DGly**) reaction is the most favorable, **Gald** + unionized glycine (**UGly**) reaction is the second most favorable, and **Gald** + protonated glycine (**PGly**) and **Gald** + glycine zwitterion (**GlyZ**) reactions are the least favorable for the formation of 2,5-dimethyl pyrazine (**25Pz**) (Shipar, 2004a). The gaseous phase reaction has been reported as more favorable than the aqueous phase (Shipar, 2004a). As **Gald** can exist in equilibrium with its keto form, i.e., 1,3-dihydroxyacetone or dihydroxyacetone (**DHA**) (Harrold, 1991; Holum, 1996; Lozynski, Rusinska-Roszak, & Mack, 1997; Thornalley, Wolff, Crabbe, & Stern, 1984; Yaylan, Majors, & Ismail, 1999), it is also necessary to evaluate the possibility of the formation of **Pz**s in the Maillard reaction involving **DHA**. Under different pH conditions, **DHA** can react with unprotonated glycine ($H_2N–CH_2–CO_2H$, **UGly**) (Harrold, 1991; Holum, 1996), protonated glycine ($H_3N^+–CH_2–CO_2H$, **PGly**) (Harrold, 1991; Holum, 1996), deprotonated glycine ($H_2N–CH_2–CO_2:^-$, **DGly**) (Eskin, 1990) and glycine zwitterion ($H_3N^+–CH_2–CO_2:^-$, **GlyZ**) (Harrold, 1991; Holum, 1996; Macrane et al., 1993) to form the Heyns rearrangement products (**HRP**s) in the initial stage (Shipar, 2006), which can consequently produce methyl glyoxal (**MG**) in the intermediate stage of the maillard reaction (Shipar, 2005). **MG** can participate in further reactions to produce **Pz**s, and this stage in the reaction can be termed as the final stage. In this paper, mechanisms for the final stage of **DHA** + **Gly** Maillard reaction under different pH conditions are proposed, following the Hodge-scheme (Hodge, 1953), and are described. During proposing the mechanisms, formation of **25Pz** is considered as one of the possible final Maillard flavor compounds in the reaction. At the standard state, Density functional computational calculations have been performed on the proposed mechanisms and the possibility of the formation of different compounds under different pH conditions has been evaluated by estimating the Gibbs free energy changes (ΔG°) for different steps of the reaction. Electronic energy changes (ΔE°) have also been calculated to observe the internal energy changes during the reaction. The total mass balance of the reaction, related to the energy changes, has always been maintained during the calculation of ΔG° and ΔE°.

The final stage of the reation can involve mainly the Strecker degradation, leading to the formation of aminoacetone (**Aace**), and self-condensation, leading to the formation of 2,5-dimethyl-3,6-dihydro-pyrazine (**36Pz**). Oxidation can take place subsequently, through which **25Pz** can be produced from **36Pz**.

The Strecker degradation in **DHA** + **UGly** reaction (Fig. 1) can involve the nucleophilic addition of **MG** (produced in the intermediate stage (Shipar, 2005)) and **UGly** (reproduced in the intermediate stage (Shipar, 2005)), resulting in the production of the addition compound, **MGadd** (1-glycino-1-hydroxy-prop-2-one or 1-glycino-1-hydroxy-acetone). Through the elimination of one molecule of water (H_2O) from **MGadd**, the Schiff base, **MGSB**, is formed. Decarboxylation of **MGSB** can lead to the production of 1-methylimino-2-ol-prop-1-ene, **MEne**, and intramolecular rearrangement (**IMR**) of **MEne** can produce 1-methylimino-prop-2-one, **MOne** (1-methylimino-acetone-2). Through protonation, **MOne** can produce a nitro-cationic adduct, **MCatN**, which can be rearranged to another carbo-cationic adduct, **MCatC**, through **IMR**. Nucleophilic addition of a hydroxide ion (OH^-) to the positively charged C-atom of **MCatC** may lead to the formation of glycino-acetone, **Gace** (1-methyl-hydroxy-amine-prop-2-one or 1-glycino-acetone). The loss of the Strecker aldehyde, formaldehyde (H_2CO), from **Gace** can follow the formation of amino-acetone, **Aace** (1-amino-prop-1-one or 1-amino-acetone).

The Strecker degradation in **DHA** + **PGly** reaction (Fig. 2) may follow the nucleophilic addition of **PGly** (reproduced in the intermediate stage (Shipar, 2005)) to **MG** (produced in the intermediate stage (Shipar, 2005)), causing the production of the ionic addition adduct, **MGadd**(**PGly**) (nitro-cationic adduct of 1-glycino-1-hydroxy-propanone or 1-protonated glycino-1-hydroxy-prop-2-one or 1-protonated glycino-1-hydroxy-acetone), which can eliminate one molecule of H_2O to produce the Schiff base, **MGSB**(**PGly**). Through decarboxylation, **MGSB**(**PGly**) can produce the ionic adduct of 1-methylimino-2-ol-prop-1-ene, **MEne**(**PGly**), which can be rearranged to **MCatN** through **IMR** **MCatN** can lead to the formation of **Aace** by following the similar mechanism proposed for **DHA** + **UGly** reaction (Fig. 1).

In the Strecker degradation of **DHA** + **DGly** (Fig. 3), MG (formed in the intermediate stage (Shipar, 2005)) and **DGly** (regenerated in the intermediate stage (Shipar, 2005)) may form an ionic addition adduct, **CatMG**(**DGly**), through nucleophilic addition reaction. **IMR** of **CatMG**(**DGly**) can take place and **MGadd**(**DGly**) can be produced, which can form the Schiff base, **MGSB**(**DGly**), through the elimination of one molecule of H_2O. Decarboxylation can take place and **MGSB**(**DGly**) can produce the ionic adduct of 1-methylimino-2-ol-prop-1-ene,

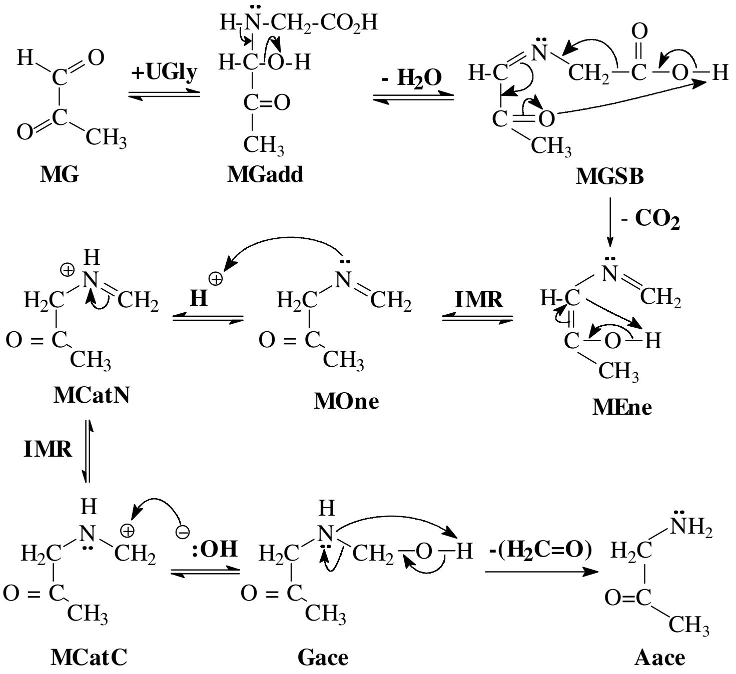


Fig. 1. Proposed mechanism for fee Strecker degradation in the final stage of **DHA** + **UGly** Maillard reaction. *Abbreviations.* **MG**, methyl glyoxal (2-keto-propanal); **UGly**, unionized or unprotonated glycine; **MGadd**, addition compound of **MG** and **UGly** (1-glycino-1-hydroxy-prop-2-one or 1-glycino-1-hydroxy-acetone); **MGSB**, Schiff base of **MGadd**; **MEne**, 1-methylirnino-2-ol-prop-1-ene; **MOne**, 1-methylimino-prop-2-one (1-methylimino-acetone-2); **MCatN**, a nitro-cationic adduct of **MOne**; **MCatC**, a carbo cationic adduct of **MOne**; **Gace**, glycino-acetone (1-methyl-hydroxy-amine-prop-2-one or 1-glycino-acetone); **Aace**, amino-acetone (1-amino-prop-1-one or 1-amino-acetone); **IMR**, intramolecular rearrangement.

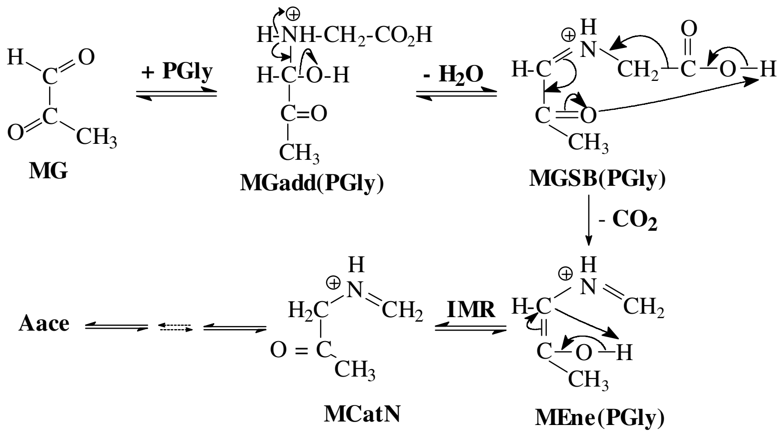


Fig. 2. Proposed mechanism for the Strecker degradation in the final stage of **DHA** + **PGly** Maillard reaction. The rest of the mechanism is as same as shown in Fig. 1. *Abbreviations.* **PGly**, protonated glycine; **MGadd(PGly)**, ionic addition adduct of **MG** and **PGly** (nitro-cationic adduct of 1-glycino-1-hydroxy-propanone or 1-protonated glycino-1-hydroxy-prop-2-one or 1-protonated glycino-1-hydroxy-acetone); **MGSB(PGly)**, Schiff base of **MGadd(PGly)**; **MEne(PGly)**, an ionic adduct of **MEne**. For other abbreviations, see the caption of 1.

MEne(DGly). Protonation of **MEne(DGly)** may lead to the production of **MOne**. Addition of one molecule of H_2O to **MOne** can form **Gace**, which can consequently produce **Aace** through the elimination of H_2CO.

In the Strecker degradation of **DHA** + **GlyZ** (Fig. 4) nucleophilic attack on the -CHO carbonyl carbon of **MG** (produced in the intermediate stage (Shipar, 2005)) by **GlyZ** (reproduced in the intermediate stage (Shipar, 2005)) can cause the production of the ionic addition adduct, **MGadd(GlyZ)**, which can form the Schiff base, **MGSB(GlyZ)**, by the elimination of one molecule of H_2O. Through decarboxylation, **MGSB(GlyZ)** can result in the production of **MOne**. Subsequent formation of **Aace** from **MOne** can follow the same pathway as proposed for **DHA** + **DGly** reaction (Fig. 3).

As **Aace** is the common product in the Strecker degradation, it can follow the same mechanism for the self-condensation and oxidation in the final stage of **DHA** + **Gly** reaction under different conditions. In the self-condensation (Fig. 5), two molecules of **Aace** can produce the

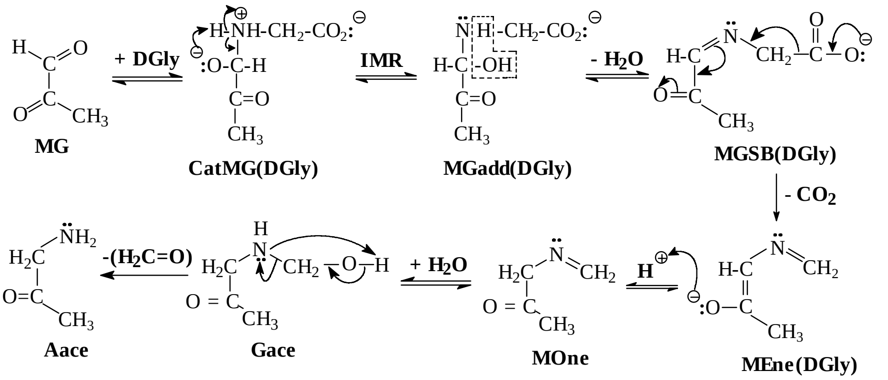


Fig. 3. Proposed mechanism for the Strecker degradation in the final stage of **DHA** + **DGly** Maillard reaction. Rest of the mechanism is as same as shown in Fig. 1. *Abbreviations*. **DGly**, deprotonated glycine; **CatMG(DGly)**, an ionic addition adduct of **MG** and **DGly**; **MGadd(DGly)**, addition compound of **MG** and **DGly** (1-deprotonated-glycino-1-hydroxy-propanone); **MGSB(DGly)**, Schiff base of **MGadd(DGly)**; **MEne(DGly)**, an ionic adduct of **MEne**. For other abbreviations, see the caption of Fig. 1.

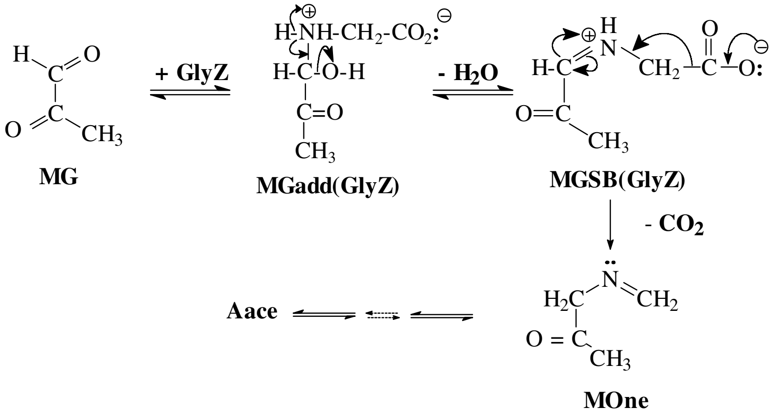


Fig. 4. Proposed mechanism for the Strecker degradation in the final stage of **DHA** + **GlyZ** Maillard reaction. The rest of the mechanism is as same as shown in Fig. 3. *Abbreviations*. **GlyZ**, glycine zwitterion; **MGadd(GlyZ)**, ionic addition adduct of **MG** and **GlyZ**; **MGSB(GlyZ)**, Schiff base of **MGadd(GlyZ)**. For other abbreviations, see the captions of Fig. 1.

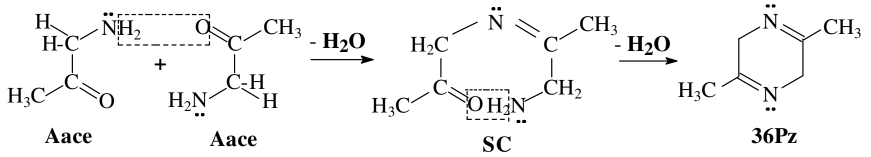


Fig. 5. Proposed mechanism for the self-condensation in the final stage of **DHA** + **Gly** Maillard reaction. *Abbreviations*. **Aace**, amino-acetone (1-amino-prop-1-one or 1-amino-acetone); **SC**, intermediate self-condensation product; **36Pz**, 2,5-dimethyl-3,6-dihydro- pyrazine.

intermediate self-condensation product, **SC**, through the elimination of one molecule of H_2O. Through the elimination of another molecule of H_2O, **SC** can lead to the production **36Pz**. Finally, **36Pz** can be oxidized to **25Pz** in the presence of air or oxygen (Fig. 6).

2. Methodology

At the standard state, all compounds in the proposed mechanisms (Figs. 1–6) have been studied in their gaseous and aqueous phases. As all compounds in the proposed

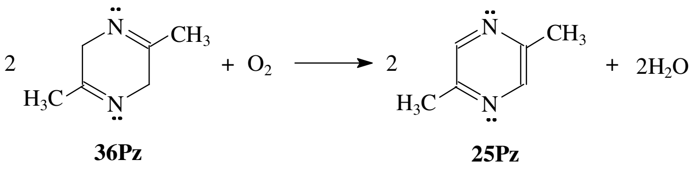


Fig. 6. Proposed mechanism for the oxidation of 2,5-dimethyl-3,6-dihydro-pyrazine (**36Pz**) to 2,5-dimethyl pyrazine (**25Pz**).

mechanisms can have many conformations in both of the gaseous and aqueous states (Csaszar, 1992; Davídek et al., 1990; Eskin, 1990; Hu, Shen, & Schaefer, 1993; Jensen & Gordon, 1991; Kobayashi & Takahashi, 1979; Lelj, Adamo, & Barone, 1994; Lozynski et al., 1997; Macrane et al., 1993; Palla, Petrongolo, & Tomasi, 1980; Ramek, Cheng, Frey, Newton, & Schäfer, 1991; Wagen et al., 1994; Yaylan et al., 1999), it is not possible to consider all of these conformations during the calculation of energy changes for different steps of a reaction, especially When it is a complex one, such as the Maillard reaction. Therefore, general optimized structures of all compounds at a specific method (RB3LYP) in the GAUSSIAN 98 program have been used in both of the gaseous and aqueous phases to avoid complexities and simplify the calculation. (Becke, 1992a, 1992b, 1993, 1996; Foresman & Frisch, 1996; Frisch & Foresman, 1998; Hehre, Radom, Schleyer, & Pople, 1986; Larid, Ross, & Ziegler, 1996; Miertus & Tomasi, 1982; Miertus, Scrocco, & Tomasi, 1981; Salahub et al., 1991; Springborg, 1995; Young, 2001). For all calculations, the 6-31G(d) polarized basis set has been used (Foresman & Frisch, 1996; Frisch & Foresman, 1998; Hehre et al., 1986; Young, 2001). During optimization, all structural parameters, e.g., bond lengths, bond angles and dihedral angles, have been used as variables. All RB3LYP/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°), in the gaseous and aqueous phases, respectively (Foresman & Frisch, 1996; Frisch & Foresman, 1998). Opt. = *Z*-matrix and/or Freq. = NoRaman keywords have been used when necessary (Foresman & Frisch, 1996; Frisch & Foresman, 1998). Single point energy calculations in the gaseous and aqueous phases have been performed on the RB3LYP/6-31G(d) optimized structures by using RB3LYP/6-31G(d) and PCM/RB3LYP/6-31G(d), respectively (Foresman & Frisch, 1996; Frisch & Foresman, 1998). The dielectric constant, $\varepsilon = 78.39$ has been used to represent the aqueous solution (Foresman & Frisch, 1996; Frisch & Foresman, 1998). Relevant ZPE have been added to the single point energies to get the total electronic energies (E°). Finally, to evaluate the internal energy changes and possibility of the formation of different compounds, electronic and free energy changes ($\Delta E^\circ = E^\circ_{\text{Product(s)}} - E^\circ_{\text{Reactant(s)}}$, and $\Delta G^\circ = G^\circ_{\text{Product(s)}} - G^\circ_{\text{Reactant(s)}}$, respectively) for different compounds in the proposed mechanisms (Figs. 1–6) have been calculated by following the total mass balance for different steps of the reaction.

3. Results and discussion

At a constant temperature and pressure, the value of ΔG indicates the position of equilibrium of the reaction, from which the spontaneity of the reaction can be predicted, whereas the value of ΔE indicates the internal energy changes during the reaction. The final stage of the Maillard reaction, involving the Strecker degradation, self-condensation and subsequent oxidation, is important for the production of flavors, aromas, and so on, which are generally unsaturated, nitrogenous compounds with high molecular weights, and are broadly known as melanoidins (Davídek et al., 1990; Eskin, 1990; Holum, 1996; Macrane et al., 1993). Formation of these compounds is caused by the polymerization of unsaturated carbonyl compounds, and the mechanism is complex because of the involvement of various reactants (Davídek et al., 1990; Eskin, 1990; Hayase, 1996; Holum, 1996; Macrane et al., 1993). ΔG° for the formation of different compounds in the proposed mechanisms (Figs. 1–6) for the final stage of **DHA + Gly** reaction under different pH conditions are presented in Table 1, obtained by using **DHA + Gly** total free energies ($G^\circ_{\text{DHA}} + G^\circ_{\text{UGly/PGly/DGly/GlyZ}}$ (Shipar, 2006)) as the standard in the equation $\Delta G^\circ = G^\circ_{\text{Product(s)}} - G^\circ_{\text{Reactant(s)}}$. ΔE° for the formation of different compounds in the proposed mechanisms are presented in Table 2, calculated by using **DHA + Gly** total electronic energies ($E^\circ_{\text{DHA}} + E^\circ_{\text{UGly/PGly/DGly/GlyZ}}$ (Shipar, 2006)) as the standard in the equation $\Delta E^\circ = E^\circ_{\text{Product(s)}} - E^\circ_{\text{Reactant(s)}}$. The dipole moments ($\mu$) and heats of formation ($\Delta H^\circ_{\text{f}}$) of different compounds are presented in Table 3.

The total mass balance of any reaction is important as it is related to the energy changes. The total mass balance of the reaction under different pH conditions have been maintained during the calculation of ΔE° and ΔG°. The main problem in balancing the total mass arises for the protonation ($+\text{H}^+$), deprotonation ($-\text{H}^+$), and the addition or elimination of OH^- ($+\text{OH}^-$ or $-\text{OH}^-$), and therefore, the following equations have been applied during balancing the total mass

$$\underset{\text{Proton}}{\text{H}^+} + \underset{\text{Water}}{\text{H}_2\text{O}} \leftrightarrow \underset{\text{Hydroxonium ion}}{\text{H}_3\text{O}^+} \qquad \text{(protonation and deprotonation)}$$

$$\text{H}_3\text{O}^+_{\text{Hydroxonium ion}} + \underset{\text{Hydroxide ion}}{\text{OH}^-} \leftrightarrow \underset{\text{water}}{2\text{H}_2\text{O}}$$

$$\text{(addition and elimination of OH}^-\text{)}$$

According to ΔG° (Table 1), except **MOne**, **MCatN** and **Gace**, the gaseous phase **DHA + UGly** reaction is favorable for the formation of all other compounds in the proposed mechanisms (Figs. 1, 5 and 6). Therefore, it is possible that in **DHA + UGly** gaseous phase reaction, protonation and **IMR** of the subsequently produced **MEne** take place at the same time, leading to the formation of **MCatC**, instead of the formation of **MOne** and **MCatN**. Nucleophilic addition of OH^- and elimination of H_2CO may take place at the same time, resulting in the production of **Aace** from **MCatC**, instead of the production of **Gace**. **Aace** can consequently form **25Pz** through the proposed mechanisms (Figs. 5 and 6). On the other hand, except **MCatN** and **Gace**, **DHA + UGly** aqueous phase reaction is favorable for the formation of all other compounds in the proposed mechanisms (Table 1, Figs. 1, 5 and 6). Therefore, in the aqueous phase **DHA + UGly** reaction, protonation of the subsequently produced **MOne** may lead to the direct

Table 1
ΔG° (in kJ/mol) for the formation of different compounds through the Strecker degradation, self-condensation and oxidation in the final stage of **DHA + Gly** Maillard reaction under different conditions, calculated by using **DHA + Gly** total free energies ($G^\circ_{DHA} + G^\circ_{uGly/pGly/DGly/GlyZ}$, Shipar, 2006) as the standard in the equation $\Delta G^\circ = G^\circ_{Product(s)} - G^\circ_{Rectant(s)}$

Reactions→	**DHA + UGly**		**DHA + PGly**	
	Gaseous	Aqueous	Gaseous	Aqueous
MG (Shipar, 2005)	−55.5	−45.3	−55.2	−45.2
MGadd	−38.7	−28.5	–	–
MGadd(PGly)	–	–	−44.3	−7.1
MGSB	−22.0	−37.3	–	–
MGSB(PGly)	–	–	−26.5	17.7
MEne	−102.0	−18.8	–	–
MEne(PGly)	–	–	−93.8	−29.1
MOne	472.7	−62.9	–	–
MCatN	407.3	622.4	365.4	−101.4
MCatC	−28.3	−364.4	−578.4	699.6
Gace	144.7	276.6	207.7	233.5
Aace	−133.1	−96.1	59.9	−42.1
SC	−218.4	−146.2	167.6	218.2
36Pz	−225.5	−171.4	160.5	−63.5
25Pz	−1365.2	−933.0	−263.4	−717.2
	DHA + DGly		**DHA + GlyZ**	
MG (Shipar, 2005)	−55.8	−45.5	−55.0	−45.0
CatMG(DGly)	−104.7	135.7	–	–
MGadd(DGly)	−119.8	132.7	–	–
MGadd(GlyZ)	–	–	216.7	199.8
MGSB(DGly)	115.2	189.4	–	–
MGSB(GlyZ)	–	–	−103.4	−7.0
MEne(DGly)	−61.1	−5.0	–	–
MOne	−330.5	−2.9	−12.1	124.3
Gace	276.6	358.9	11.4	−362.3
Aace	−941.2	−245.4	−215.5	−67.8
Sc	−1834.6	−444.8	−383.3	−89.6
36Pz	−1841.7	−470.1	−390.3	−114.9
25Pz	−4267.8	−1530.3	−1035.5	−819.9

For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 1–6.

production of **MCatC**, instead of the production of **MCatN**. Nucleophilic addition of OH^- and elimination of H_2CO may occur at the same time, leading to the formation of **Aace** from **MCatC**, instead of the formation of **Gace** and **Aace** can produce **Pz**s through the proposed mechanisms presented in Figs. 5 and 6.

Based on ΔG° (Table 1), **DHA + PGly** gaseous phase reaction has been found not to be favorable for the formation of **MCatN**, **Gace**, **Aace**, **SC** and **36Pz** in the proposed mechanisms (Figs. 2, 5 and 6). Hence, the consequently produced **MEne**(**PGly**) under this condition may produce **MCatC**, instead of the formation of **MCatN**, by following protonation and **IMR** at the same time. **MCatC** may follow some other mechanisms to produce **Pzs**. The aqueous phase **DHA + PGly** reaction is not feasible for the formation of **MGSB**(**PGly**), **MCatC**, **Gace** and **SC** (Figs. 2 5 and 6). Therefore, elimination of H_2O and CO_2 from the subsequently produced **MGadd**(**PGIy**) under these conditions may take place at the same time, leading to the formation of **MEne**(**PGly**) instead of the formation of **MGSB**(**PGly**), which can consequently form **MCatN** (Fig. 2). Nucleophilic addition of OH^- and elimination of H_2CO may occur at the same time, leading to the formation of **Aace** from **MCatN** instead of the formation of **MCatC** and **Gace**. **Aace** may follow some other mechanisms to produce **Pz**s.

DHA + DGly reaction is assumed not to be favorable for the formation of **Gace** in the gaseous state, and **CatMG(DGly), MGadd**(**DGly**) and **MGSB**(**DGly**) in the aqueous state (Table 1, Figs. 3, 5 and 6). Therefore, addition of H_2O and elimination of H_2CO may occur at the same time, leading to the formation of **Aace** from the consequently produced **MOne**, instead of the formation of **Gace** in the gaseous state. On the other hand, nucleophilic addition of **DHA** and **DGly** in the aqueous state may follow the protonation and elimination of H_2O and CO_2 at the same time, resulting in the production of **MEne**(**DGly**), which can consequently produce **Aace** though the proposed mechanisms (Fig. 3). **Aace** can produce **Pz**s through the proposed mechanisms as presented in Figs. 5 and 6.

DHA + GlyZ reaction has been found not to be feasible for the formation of **MGadd**(**GlyZ**) and **Gace** in the gaseous state, and **MGadd**(**GlyZ**) and **MOne** in the aqueous state (Table 1 and Figs . 4–6). Therefore, it is possible that nucleophilic addition of **DHA** and **GlyZ** and elimination of H_2O may occur at the same time in the gaseous

Table 2
ΔE° (in kJ/mol) for the formation of different compounds through the Strecker degradation, self-condensation and oxidation in the final stage of **DHA + Gly** Maillard reaction under different conditions, calculated by using **DHA + Gly**total free energies ($E^\circ_{\mathrm{DHA}} + E^\circ_{\mathrm{uGly/pGly/DGly/GlyZ}}$, Shipar, 2006) as the standard in the equation $\Delta E^\circ = E^\circ_{\mathrm{Product(s)}} - E^\circ_{\mathrm{Rectant(s)}}$

Reactions→	**DHA + UGly**		**DHA + PGly**	
	Gaseous	Aqueous	Gaseous	Aqueous
MG (Shipar, 2005)	−13.3	−3.58	−10.1	−0.8
MGadd	−46.8	−36.5	–	–
MGadd(PGly)	–	–	−34.6	−17.7
MGSB	14.9	−0.32	–	–
MGSB(PGly)	–	–	27.6	51.0
MEne	−32.8	5.2	–	–
MEne(PGly)	–	–	172.3	244.9
MOne	152.0	174.2	–	–
MCatN	357.4	93.1	571.9	148.0
MCatC	−131.9	84.6	82.5	139.5
Gace	90.4	111.5	304.8	166.4
Aace	55.9	−18.7	36.2	133.5
SC	−75.5	−3.3	106.5	353.5
36Pz	−51.6	2.5	377.4	112.3
25Pz	−636.0	−651.2	221.9	39.4
	DHA + DGly		**DHA + GlyZ**	
MG (Shipar, 2005)	−13.5	−3.6	−8.8	−2.4
CatMG(DGIy)	−54.8	−39.0	–	–
MGadd(DGly)	−68.7	−41.9	–	–
MGadd(GlyZ)	–	–	200.4	183.7
MGSB(DGly)	−24.9	14.8	–	–
MGSB(GlyZ)	–	–	−79.7	16.6
MEne(DGly)	110.5	172.8	–	–
MOne	−597.8	99.7	70.8	203.8
Gace	−659.4	37.0	9.2	141.0
Aace	−805.7	−93.2	−137.1	10.9
Sc	−175.0	152.2	−237.8	55.8
36Pz	−151.1	−146.4	−213.9	61.6
25Pz	−3635.1	−4809.2	−960.8	−4393.0

For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 1–6.

Table 3
Dipole moments (μ, in Debye) and heats of formation ($\Delta H^\circ_{\mathrm{f}}$, in kJ/mol) of different compounds presented in Figs. 1–6

Compounds↓	μ		$\Delta H^\circ_{\mathrm{f}}$ [AMI]
	Gaseous [RB3LYP/6-31 G(d)]	Aqueous [PCM/RB3LYP/6-31G(d)]	
MG (Shipar, 2005)	0.953	1.118	−1132.191
MGadd	1.6	1.8	−709.8
MGadd(PGly)	6.9	8.2	−5.5
CatMG(DGly)	7.2	8.3	−737.64
MGadd(DGly)	10.9	12.8	−795.8
MGadd(GlyZ)	12.9	15.3	−300.9
MGSB	2.63	3.2	−411.5
MGSB(PGly)	6.6	7.9	−266.5
MGSB(DGly)	6.96	8.9	−535.6
MGSB(GlyZ)	3.6	4.03	−377.4
Mene	1.49	1.7	−53.2
MEne(PGly)	1.97	2.3	563.2
MEne(DGly)	2.2	2.6	−161.1
Mone	2.66	3.7	−62.8
MCatN	4.9	6.2	595.3
MCatC	6.1	7.02	606.2
Gace	2.6	3.2	−358.4
Aace	2.8	3.3	−174.9
SC	3.6	4.1	−115.9
36Pz	0.0	0.0	142.7
25Pz	0.0	0.0	120.5

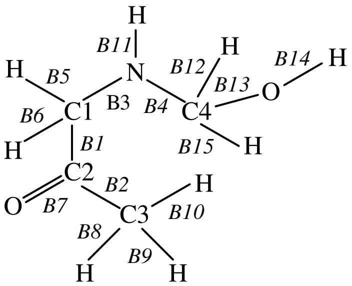
state, leading to the formation of **MGSB(GlyZ)** instead of the formation of **MGadd**(**GlyZ**). Elimination of H_2O and H_2CO from the subsequently produced **MOne** from **MGSB**(**GlyZ**) may occur at the same time, leading to the formation of **Aace** in the gaseous state. On the other hand, elimination of CO_2 and H_2O from **MGSB**(**GlyZ**) at the same time may lead to the formation of **Gace** instead of the formation of **MOne** in the aqueous state. **Gace** can form **Aace** consequently, which can produce **Pz**s through the proposed mechanisms (Figs. 5 and 6).

According to ΔE° (Table 2) of the Strecker degradation (Figs. 1–4), **MICatC** and **MGadd** are assumed to electronically be the most stable species in **DHA** + **UGly** gaseous and aqueous phase reactions, respectively. In both of the gaseous and aqueous states, **MGadd**(**PGly**) seems to electronically be the most stable species in the Strecker degradation of **DHA** + **PGly**. **Aace** has been found to electronically be the most stable species in the Strecker degradation of **DHA** + **DGly** and **DHA** + **GlyZ** in both of the gaseous and aqueous states. Adequate information on these species is still not available. Experimental detection of these compounds in the reaction is assumed difficult as they readily undergo further reactions due to their comparatively unstable nature.

Under all pH conditions, and in both of the gaseous and aqueous states, **Gace** appears electronically to be less stable than **Aace** (Table 2). Therefore, **Aace**, formed through the Strecker degradation of **MG** and **Gly** species (Figs. 1–4), is assumed the most likely precursor for the formation of pyrazine rings in the self-condensation (Fig. 5). Sufficient data on these species are still not available. In both of the gaseous and aqueous states, **DHA** + **DGly** reaction is assumed the most feasible for the production of **Aace**, and the gaseous state reaction is more favorable than that of the aqueous state (Table 1). In producing **Aace**, **DHA** + **GlyZ** and **DHA** + **UGly** reactions are the second most favorable in the gaseous and aqueous states, respectively (Table 1). **DHA** + **PGly** reaction is not feasible for the production of **Aace** in the gaseous state (Table 1). Therefore, the gaseous phase **DHA** + **PGly** reaction is assumed to be more hindered than that of the aqueous phase in producing **Pz**s. **DHA** + **GlyZ** reaction is found to be favorable for the production of **Aace** in both of the gaseous and aqueous states (Table 1). According to ΔE°. (Table 2), **Aace** is electronically more stable in the gaseous state reaction than in the aqueous state under all pH conditions. Geometric parameters of **DHA**, **Gly** species and **MG** have been reported previously (Shipar, 2006, 2005). Some important geometric parameters of **Gace** and **Aace**, used in the present study, are presented in Figs. 7 and 8, respectively.

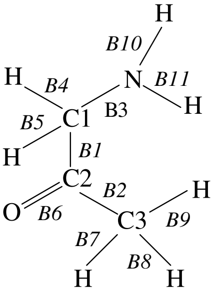
The gaseous state reaction is found to be more favorable than the aqueous state reaction in producing **SC** under all conditions (Table 1). However, both of the gaseous and aqueous phase **DHA** + **PGly** reactions are not favorable for the formation of **SC** (Table 1). Based on ΔE° (Table 2), **SC** is electronically more unstable in the gaseous state than the aqueous state reaction under all pH conditions.

Except for the **DHA** + **PGly** reaction, the gaseous phase reaction is found to be more favorable than the aqueous phase reaction in producing **36Pz** (Table 1). According to ΔE°, **36Pz** is electronically more stable in the gaseous phase **DHA** + **UGly**, **DHA** + **DGly** and **DHA** + **GlyZ** reactions than in the aqueous phase reactions and more stable in the aqueous phase **DHA** + **PGly** reaction than in the gas-



B1= 1.5363 Å,*B2*= 1.5167 Å,*B3* = 1.4511 Å, *B4* = 1.4642 Å,*B5* = 1.1019 Å,*B6* = 1.0987 Å, *B7* = 1.2176 Å,*B8* = 1.092 Å,*B9* = 1.0981 Å, *B10* = 1.0966 Å,*B11* = 1.021 Å,*B12* = 1.1049 Å, *B13* = 1.4092 Å,*B14* = 0.9692 Å,*B15* = 1.0956 Å, C_1-C_2-C_3 = 117.1°, C_1-C_2-O = 120.6°, C_1-N-C_4 = 113.3°, N-C_4-O = 111.6°, C_4-O-H = 108°, N-C_1-C_2-O = -10.3°, N-C_1-C_2-C_3 = 171°, N-C_4-O-H = -79.7°.

Fig. 7. RB3LYP/6-31G(d) (geometric parameters of glycino-acetone (**Gace**).



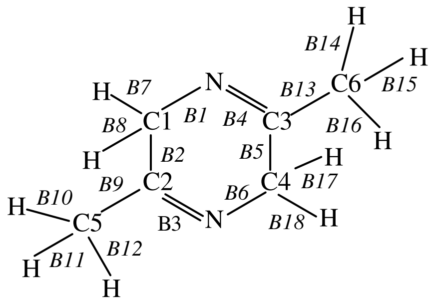
B1= 1.5261 Å,*B2*= 1.5156 Å,*B3* = 1.4528 Å, *B4* = 1.1085 Å,*B5* = 1.1006 Å,*B6* = 1.217 Å, *B7* = 1.0979 Å,*B8* = 1.0961 Å,*B9* = 1.0919 Å, *B10* = 1.0192 Å,*B11* = 1.0157 Å, C_1-C_2-C_3 = 116.8°, C_1-C_2-O = 121°, C_1-N-H = 107.9°, C_1-N-H = 111.1°, N-C_1-C_2-O = -17.2°, N-C_1-C_2-C_3 = 163.3°.

Fig. 8. RB3LYP/6-31G(d) geometric parameters of amino-acetone (**Aace**).

eous phase reaction. Some important geometric parameters of **36Pz**, used in the present study, are presented in Fig. 9.

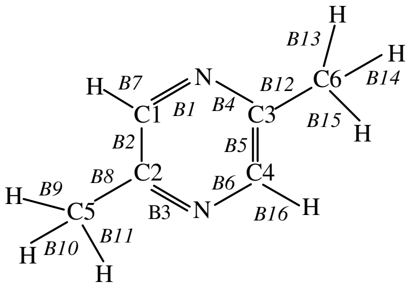
Oxidation plays an important role during the production of **25Pz** from **36Pz** (Table 1, Fig. 6). Hence, presence of air or oxygen is necessary for the production of **25Pz** as a possible Maillard flavor compound in **DHA + Gly** reactions. In both of the gaseous and aqueous states, **DHA + DGly** reaction is assumed the most favorable for the production of **25Pz**, and the gaseous phase reaction is assumed to be more favorable than the aqueous phase reaction in producing **25Pz**. Though the effect of pH in the Maillard reaction is not clear-cut or obvious at all, the present evaluation is apparently consistent with the prior findings that the possibility of the existence of sugars in their reducing forms is generally increased at high pH or under basic conditions, and therefore, the rate of browning usually increases (Ames, 1990; Bell, 1997; Davídek et al., 1990; Eskin, 1990; Lea & Hannan, 1949; Macrane et al., 1993). The **DHA + UGly** reaction is the second most favorable for the production of **25Pz**, and the gaseous phase is also more favorable than the aqueous phase reaction (Table 1). **DHA + GlyZ** and **DHA + PGly** reactions are assumed to be the third most and least favorable for the formation of **25Pz**, respectively, and the gaseous and aqueous states are more plausible in producing **25Pz** under these conditions, respectively (Table 1). As the gaseous phase **DHA + PGly** reaction is not favorable for the formation of **Aace** and **36Pz** (Table 1), the precursor of **25Pz**, formation of **25Pz** under this condition is assumed much more hindered than that of the others. The aqueous phase **DHA + PGly** reaction is found to be favorable for the formation of **Aace** and **36Pz**, and therefore formation of **25Pz** under this condition is assumed to follow some other mechanism. However, it is in agreement with the previous reports that the Maillard reaction is usually not favorable at low pH or under acidic conditions (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). In both of the gaseous and aqueous states, the **DHA + GlyZ** reaction has been reported as not to be favorable for the production of **HRPs** (Shipar, 2006). Therefore, the reaction under this condition may involve some other mechanisms, especially in the initial stage. According to ΔE° (Table 2), **25Pz** is electronically more stable in the aqueous state reaction than the gaseous state, and is electronically less energetic than **36Pz** in both of the gaseous and aqueous state reactions under all conditions. Some important geometric parameters of **25Pz**, used in the present study, are presented in Fig. 10.

According to the total mass balance, water is a by-product in **DHA + Gly** reactions under all conditions during the formation of **Pz**s. During the formation of **36Pz**, a total of five molecules of water are produced as by-product than the initiation step of **DHA + UGly** reaction (Shipar, 2006), whereas six molecules are produced for each of the **DHA + PGly**, **DHA + DGly** and **DHA + GlyZ** reactions. On the other hand, for the production of **25Pz**, a total six molecules of water are found to be produced as by-products of the initiation step of the **DHA + UGly** reaction (Shipar, 2006), whereas a total seven molecules are produced for each of **DHA + PGly**, **DHA + DGly** and **DHA + GlyZ** reactions. It is in agreement with the previous statements that water is a by-product in the Maillard reaction (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993).



B1 = 1.4569 Å, *B2* = 1.5163 Å, *B3* = 1.2753 Å,
B4 = 1.2753 Å, *B5* = 1.5163 Å, *B6* = 1.4569 Å,
B7 = 1.1011 Å, *B8* = 1.1011 Å, *B9* = 1.5079 Å,
B10 = 1.0982 Å, *B11* = 1.0922 Å, *B12* = 1.0982 Å,
B13 = 1.5079 Å, *B14* = 1.0922 Å, *B15* = 1.0982 Å,
B16 = 1.0982 Å, *B17* = 1.1011 Å, *B18* = 1.1011 Å,
C_1-C_2-N = 124.7°, C_1-C_2-C_5 = 116.3°, C_1-N-C_3 = 118.1°, C_3-C_4-N = 117.2°, N-C_3-C_6 = 119°, N-C_1-C_2 = 0°, N-C_1-C_2-C_5 = 180°, N-C_3-C_4-N = 0°, C_1-N-C_3-C_6 = 180°.

Fig. 9. RB3LYP/6-31G(d) (geometric parameters of 2,5-dimethyl-3,6-dihydro-pyrazine (**36Pz**).



B1 = 1.3346 Å, *B2* = 1.4018 Å, *B3* = 1.3424 Å,
B4 = 1.3424 Å, *B5* = 1.4018 Å, *B6* = 1.3346 Å,
B7 = 1.0893 Å, *B8* = 1.5058 Å, *B9* = 1.0942 Å,
B10 = 1.0958 Å, *B11* = 1.0959 Å, *B12* = 1.5058 Å,
B13 = 1.0958 Å, *B14* = 1.0942 Å, *B15* = 1.0959 Å,
B16 = 1.0893 Å, C_1-C_2-N = 120°, C_1-C_2-C_5 = 122.3°, C_1-N-C_3 = 117°, C_3-C_4-N = 123°, N-C_3-C_6 = 118°, N-C_1-C_2-N = 0°, N-C_1-C_2-C_5 = 180°, N-C_3-C_4-N = 0°, C_1-N-C_3-C_6 = 180°.

Fig. 10. RB3LYP/6-31G(d) geometric parameters of 2,5-dimethyl pyrazine (**25Pz**).

4. Conclusion

Density functional computations have been performed at the standard state on the proposed mechanisms for the final stage of **DHA + Gly** reaction under different pH conditions. Formation of **25Pz** has been considered as one of the possible final Maillard flavor compound during proposing the mechanisms, and the Hodge-scheme (Hodge, 1953) has generally been followed. ΔE° and ΔG° for the formation of different compounds in different steps of the proposed mechanisms have been calculated by following the total mass balance of different steps of the reaction. Thus, the possibility of the formation of different compounds through different steps has been tested. In both of the gaseous and aqueous states, **DHA + DGly**, **DHA + UGly**, **DHA + GlyZ** and **DHA + PGly** reactions have been found to be the most, second most, third most, and least favorable for the formation of **25Pz**, respectively. In producing **25Pz**, the gaseous phase **DHA + DGly**, **DHA + UGly** and **DHA + GlyZ** reactions have been assumed more feasible than the aqueous phase reactions whereas the **DHA + PGly** aqueous phase reaction has been found not to be feasible for the formation of **Aace** and **36Pz**, and therefore, formation of **25Pz**, i.e., the rate of browning under this condition is assumed the lowest. As the formation of **Aace** and **36Pz** has been found to be feasible in the aqueous phase **DHA + PGly** reaction, the rate of browning, i.e., the production of **25Pz**, is assumed to be the second lowest under this condition. During the production of **25PZ**, **DHA + GlyZ** reaction may involve some

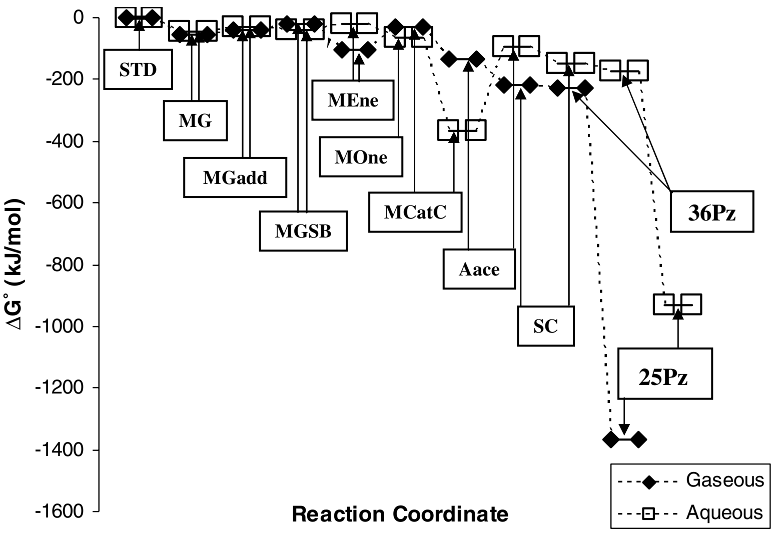


Fig. 11. Possible low energy (ΔG°) diagram for the formation of 2,5-dimethyl pyrazine in the final stage of **DHA + UGly** Maillard reaction, obtained by using **DHA + UGly** total free energies ($G^\circ_{\mathrm{DHA}} + G^\circ_{\mathrm{UGly}}$, Shipar, 2006) as the standard (**STD**). For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 1, 5 and 6.

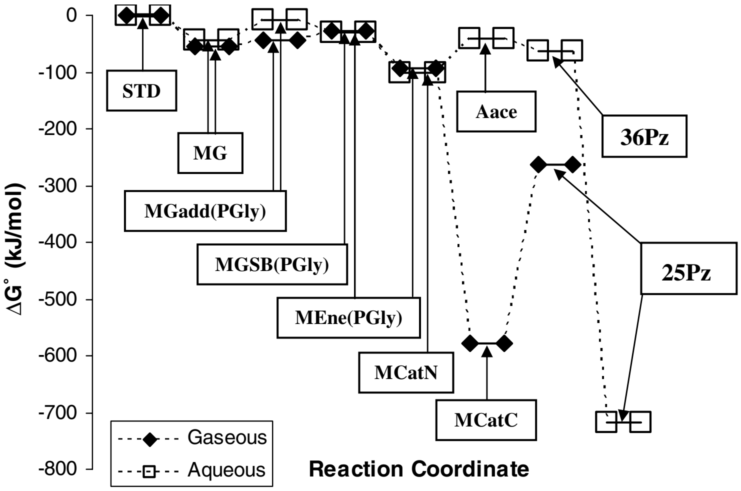


Fig. 12. Possible low energy (ΔG°) diagram for the formation of 2,5-dimethyl pyrazine in the final stage of **DHA + PGly** Maillard reaction, obtained by using **DHA + PGly** total free energies ($G^\circ_{\mathrm{DHA}} + G^\circ_{\mathrm{pGly}}$, Shipar, 2006) as the standard (**STD**). For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 2, 5 and 6.

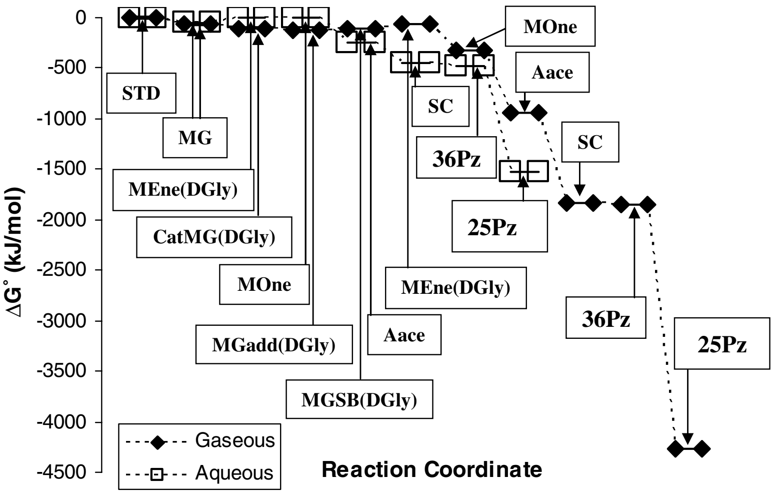


Fig. 13. Possible low energy (ΔG°) diagram for the formation of 2,5-dimethyl pyrazine in the final stage of **DHA** + **DGly** Maillard reaction, obtained by using **DHA** + **DGly** total free energies ($G^\circ_{\mathrm{DHA}} + G^\circ_{\mathrm{DGly}}$, Shipar, 2006) as the standard (**STD**). For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 3, 5 and 6.

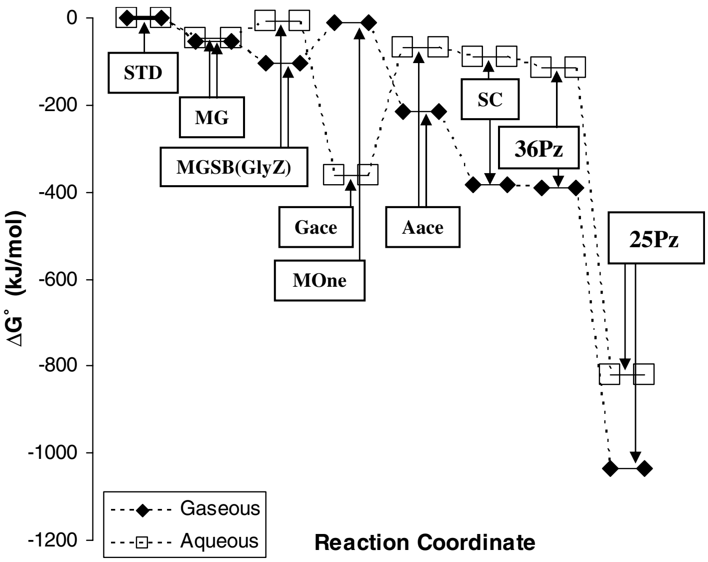


Fig. 14. Possible low energy (ΔG°) diagram for the formation of 2,5-dimethyl pyrazine in the final stage of **DHA** + **GlyZ** Maillard reaction, obtained by using **DHA** + **GlyZ** total free energies ($G^\circ_{\mathrm{DHA}} + G^\circ_{\mathrm{GlyZ}}$, Shipar, 2006) as the standard (**STD**). For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 4–6.

other critical mechanisms in the initial stage, as the reaction under this condition is not favorable for the production of **HRP**s (Shipar, 2006). **Aace**, formed through, the Strecker degradation, has been found to be the most likely precursor of the pyrazine ring in the self-condensation. The gaseous phase reaction is assumed more feasible than the aqueous phase reaction in producing **SC**. Based on ΔG°, the possible low energy diagrams for the formation of **25Pz** in **DHA** + **Gly** reaction under different pH conditions are presented in Figs. 11–14. Water has been found as a by-product, which has also been reported as necessary for the initiation of the reaction (Shipar, 2006). Oxidation plays an important role during the production of **25Pz** from **36Pz**. In comparison, the **DHA** + **Gly** reaction is apparently more feasible than **Gald** + **Gly** reaction (Shipar, 2004a) for the production of **25Pz**. Adequate information is still lacking. The present findings will be helpful for further studies in order to establish mechanisms of the reaction, leading to the control of the reaction potentially in vivo as well as in vitro. Computational studies on the Maillard reaction involving other sugars and amino compounds are also necessary to find out the similarities and variations in the mechanisms of different Maillard systems.

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