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Formation of pyrazines in hydroxyacetaldehyde and glycine nonenzymatic browning Maillard reaction: A computational study

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Abstract

By considering the formation of pyrazines ($C_4N_2H_6$ and $C_4N_2H_4$) as one of the possible final Maillard flavour compounds, Density Functional Theory computations at the standard state have been performed on the proposed mechanisms of glyoxal and glycine in the advanced stage of hydroxyacetaldehyde and glycine nonenzymatic browning reaction under different pH conditions. The results reveal that the basic condition is the most favourable for the production of pyrazines (**Pz**s), and the aqueous solution is more favourable than that of the gaseous state. The reactions at the isoelectric point of glycine and under neutral conditions are the second and third most favourable for the production of **Pz**s, respectively. The reaction under acidic conditions is the least feasible for the production of **Pz**s. Amino acetaldehyde is the most likely precursor of the pyrazine ring in the reaction. Presence of air or oxygen is necessary for the production of 2,3,5,6-tetrahydropyrazine ($C_4N_2H_4$) from 3,6-dihydropyrazine ($C_4N_2H_6$). Water is necessary with glyoxal and glycine species for the formation of **Pz**s and water is produced as a by-product during the formation of **Pz**s.

Keywords: Hydroxyacetaldehyde; Glycine; Pyrazines; Nonenzymatic browning Maillard reaction; Density functional theory computation

1. Introduction

Nonenzymatic browning, also known as the Maillard reaction (Maillard, 1912), occurs between carbonyl compounds, especially reducing sugars, and compounds with free amino groups, such as amines, amino acids, and proteins. The reaction occurs upon heating or prolonged storage, and is one of the deteriorative processes that take place in stored foods (Davdeḱ, Velśek, & Pokorný, 1990; Eskin, 1990; Macrane, Robinson, & Saadler, 1993). More recently, it has been realized that the reaction occurs in the human body, and is therefore important in medicine (Ledl & Schleicher, 1990; Meade, Miller, & Gerrard, 2003; Reber et al., 2002). Although more than 90 years have passed since the first research on the Maillard reaction, and many results have been gathered later on, there is still no widely accepted explanation of the mechanism. Several mechanisms for the Maillard reaction have been proposed (Hodge, 1953; Namiki & Hayashi, 1983; Tressl, Nittka, & Kersten, 1995). Of these, the Hodge scheme (Hodge, 1953) is still the most accepted, and has consequently been reviewed by many authors. The Maillard reaction is a complex series of chemical reactions, and due to the complexity of intermediates and final products or melanoidines, controlling the reaction associated with food quality, nutritional value, and medicinal aspects, is still a great challenge. To control the reaction, it is

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necessary for the reaction mechanism to be well studied and understood. Due to the complexity, conducting experiments and analyzing the intermediates and final product mixtures for accurate information are complicated. Though many studies have been conducted to learn the pathways leading to the formation of melanoidines, the mechanism is still obscure and proven specific pathways for the formation of Maillard colours, flavours, antioxidants, and so on are not available. Computational model chemistry could successfully be applied to such a complex reaction to obtain useful information that will be helpful to learn mechanisms to control the reaction.

Due to the links to various pathologies, interest on α-dicarbonyl compounds, e.g. glyoxal (**Gox**), has recently increased significantly. **Gox** is mutagenic, and has been detected in many foods and beverages (Bjeldanes & Chew, 1979; Moree-Testa & Saint-Jalm, 1981; Murata-Kamiya, Kamiya, Kaji, & Kasai, 1998; Sayato, Nakamuro, & Ueno, 1987). It has been implicated in many degenerative diseases as well as in the aging process through reactions with the amino residues of proteins, resulting in the formation of the advanced glycation end products (**AGE**s) (Akhand et al., 2001; Leng, Graves, & Chaires, 1998; Odani, Shinzato, Matsumoto, Usami, & Maeda, 1999; Odani et al., 1998; Sady et al., 2000; Shangari & O'Brien, 2004; Thornalley, George, & Argirov, 2000). It reacts with RNA and DNA, and modifies nucleic acid and nucleoproteins (Leng et al., 1998; Mistry et al., 1999). However, **Gox** is less reactive than the substituted methyl glyoxal in aqueous, nonenzymatic cross-linking, which may be due to the complexities of the solution structure of Gox (Meade et al., 2003). **Gox** has also been studied theoretically with different computational methods (Bulat & Toro-Labbé, 2002; Sancho-García, Peréz-Jiménez, Pérez-Jordá, & Moscardó, 2001; Tantirungrotechai, 2003; Zelek, Wasilewski, & Heldt, 2000). Previous Density Functional Theory computations at the standard state on the proposed mechanisms for the early stage of hydroxyacetaldehyde (**Hald**) and glycine (**Gly**, i.e. **UGly**, **PGly**, **DGly** and **GlyZ**; abbreviations are explained latter) nonenzymatic browning Maillard reaction under different pH conditions showed that **Gox** is one of the most likely intermediates in the reaction (Shipar, Jalbout, & Adamowicz, submitted for publication). Gaseous state reactions were more favourable than aqueous solutions for the production of **Gox**. Reactions under basic and neutral conditions were proposed to be the most and second most favourable for the formation of **Gox**, respectively. Due to low feasibility for formation of almost all intermediates in the proposed mechanisms, the reactions under acidic condition and at the isoelectric point of glycine have been assumed unfavourable for the production of **Gox**. Oxidation of **Hald** to **Gox** (**Hald** + O_2→ **Gox** + H_2O) was more plausible in the gaseous state than in aqueous solution (Shipar et al., submitted for publication). The browning activity of **Gox** has been reported as 0.515 lit/min, whereas 0.019 and 0.014 lit/min for glucose and fructose, respectively (Hayashi & Namiki, 1986; Namiki & Hayashi, 1983). **Gox**, produced in the early stage of the **Hald** + **Gly** reaction or through the oxidation of **Hald**, can readily undergo further reactions in the advance stage with the eliminated or reproduced **Gly** species (**UGly**, **PGly**, **DGly** and **GlyZ**; abbreviations are explained latter) in the early stage to produce melanoidines, such as pyrazines (**Pz**s) (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). Mechanisms for the formation of Maillard flavours and aromas, such as **Pz**s, have not been well studied or well established, and therefore, very little information on **Pz**s is available (Ho & Chen, 1999; Shu, 1999; Wilen, 1970). Production of these compounds is related to colour formation (Shibamoto & Bernhard, 1978; Wong & Shibamoto, 1996). In addition, it may affect the formation of other Maillard products, such as antioxidants, toxicants, etc. Learning the proper mechanism for the production of **Pz**s is necessary to control the Maillard reaction potentially against undesirable final products or melanoidines. The reaction tends to follow different routes at the same time to produce various melanoidines through the formation of various complex intermediates. Therefore, it is difficult to get accurate information for establishing proper mechanisms through experimental techniques. In the present study, the possibility of the formation of **Pz**s, as one of the probable final Maillard flavour compounds, is evaluated through Density Functional computations at the standard state on the proposed mechanisms for the reaction between **Gox** (produced in the early stage of **Hald** + **Gly** reaction (Shipar et al., submitted for publication)) and **Gly** species (**UGly**, **PGly**, **DGly** and **GlyZ**, reproduced in the early stage of **Hald** + **Gly** reaction (Shipar et al., submitted for publication)) under different pH conditions, usually following the Hodge-scheme (Hodge, 1953). The possibility of the production of **Pz**s in **Hald** + **Gly** or **Gox** + **Gly** reaction has not yet been studied, and therefore, the mechanism is still obscure. However, it can be assumed that during the formation of **Pz**s, the produced and/or reproduced **Gox** and **Gly** species in the early stage of the **Hald** + **Gly** reaction under different pH conditions are generally initially involved in the Strecker degradation of **Gox** and **Gly** species, leading to the formation of amino acetaldehyde (C_2NH_5O). Self-condensation of C_2NH_5O may take place latter, leading to the formation of 3,6-dihydropyrazine ($C_4N_2H_6$), and consequent oxidation of $C_4N_2H_6$ could lead to the production of 2,3,5,6-tetrahydropyrazine ($C_4N_2H_6$).

Under neutral (pH = 7) and acidic (pH < 5.5) conditions, unprotonated glycine (H_2N–CH_2–CO_2H, **UGly**) and protonated glycine (H_3N^+–CH_2–CO_2H, **PGly**) are likely to be the leading species, respectively (Harrold, 1991; Holum, 1996). Therefore, the Strecker degradation under these conditions may involve the mechanisms as presented in Fig. 1. On the other hand, deprotonated glycine (H_2N–CH_2–CO_2^-, **DGly**) and glycine zwitterion (H_3N^+–CH_2–CO_2:$^-$, **GlyZ**) become the dominant species under basic conditions (pH > 8) and at the isoelectric point of glycine (I = pH ≈ 6), respectively (Eskin, 1990; Harrold, 1991; Holum, 1996; Macrane et al., 1993). Hence, the Strecker

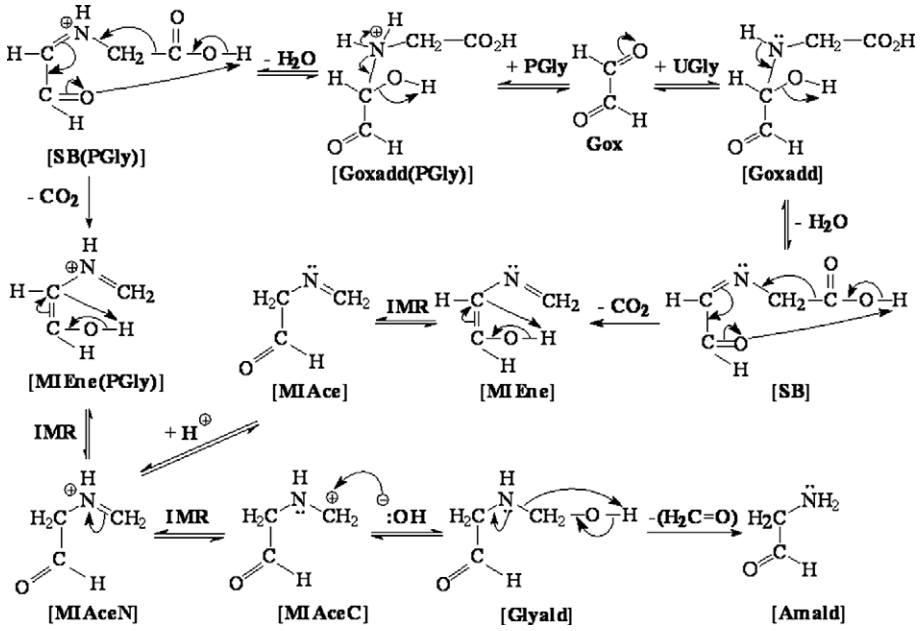


Fig. 1. Proposed mechanism for the Strecker degradation in **Gox** + **UGly** and **Gox** + **PGly** reactions. *Abbreviations*: **Gox** = glyoxal; **UGly** = unprotonated or unionized glycine; **PGly** = protonated glycine; **Goxadd** = addition compound of **Gox** and **UGly** (2-glycino-2-hydroxy acetaldehyde or 2-glycino-2-hydroxy ethanone-1); **Goxadd(PGly)** = ionic addition adduct of **Gox** and **PGly** (2-protonated glycino-2-hydroxy acetaldehyde or 2-protonated glycino-2-hydroxy ethanone-1); **SB** = Schiff base of **Goxadd** (2-glycino acetaldehyde or 2-glycino ethanone-1); **SB(PGly)** = Schiff base of **Goxadd(PGly)** [2-protonated glycino acetaldehyde or 2-protonated glycino ethanone-1]; **MIEne** = 1-methylimino-2-hydroxy ethene-1; **MIEne(PGly)** = an ionic adduct of **MIEne**; **MIAce** = 2-methylimino acetone or 2-methylimino ethanone-1; **MIAceN** = a nitro-cationic adduct of **MIAce**; **MIAceC** = a carbo-cationic adduct of **MIAce**; **Glyald** = glycino acetaldehyde (2-glycino acetaldehyde or 2-glycino ethanone-1); **Amald** = amino acetaldehyde (2-amino acetaldehyde or 2-amino ethanone-1); **IMR** = intramolecular rearrangement.

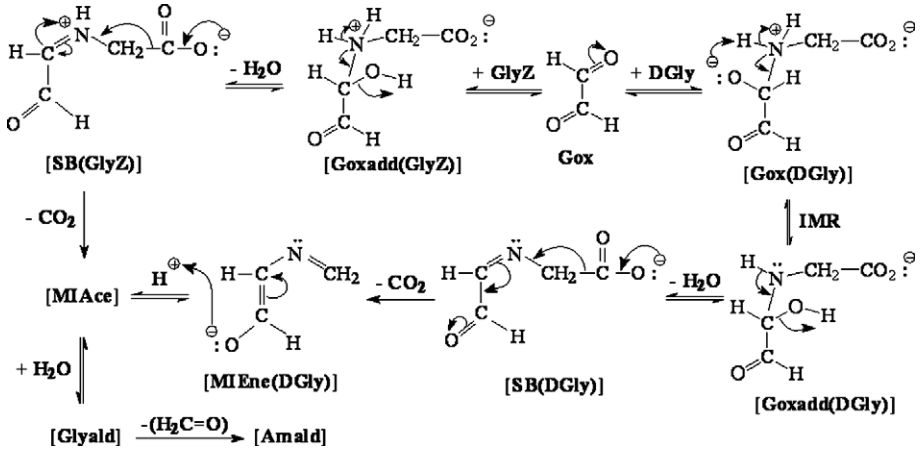


Fig. 2. Proposed mechanism for the Strecker degradation in **Gox** + **DGly** and **Gox** + **GlyZ** reactions. *Abbreviations*: **DGly** = deprotonated glycine; **GlyZ** = glycine zwitterion; **Gox(DGly)** = ionic addition adduct of **Gox** and **DGly**; **Goxadd(DGly)** = addition compound of **Gox** and **DGly** (2-deprotonated glycino-2-hydroxy acetaldehyde or 2-deprotonated glycino-2-hydroxy ethanone-1); **Goxadd(GlyZ)** = addition adduct of **Gox** and **GlyZ**; **SB(DGly)** = Schiff base of **Goxadd(DGly)** [2-deprotonated glycino acetaldehyde or 2-deprotonated glycino ethanone-1]; **SB(GlyZ)** = Schiff base of **Goxadd(GlyZ)**; **MIEne(DGly)** = an ionic adduct of **MIEne**. For other abbreviations, see the caption of Fig. 1.

degradation under these conditions can follow the mechanisms as shown in Fig. 2. Amino acetaldehyde (**Amald**) is the main product in the Strecker degradation (Figs. 1 and 2), and therefore, it can follow the same mechanism for the self-condensation under different pH conditions, leading to the formation of 3,6-dihydropyrazine (**36Pz**) (Fig. 3). Oxidation of **36Pz** can occur subsequently, and 2,3,5,6-tetrahydropyrazine (**Pz**) can be produced (Fig. 3).

2. Methodology

At the standard state, all compounds in the proposed mechanisms (Figs. 1–3) have been studied in their gaseous state and aqueous solution. As all compounds in the proposed mechanisms can have many conformations in both of the gaseous state and aqueous solution, it is not possible to consider all of these conformations during the calculation

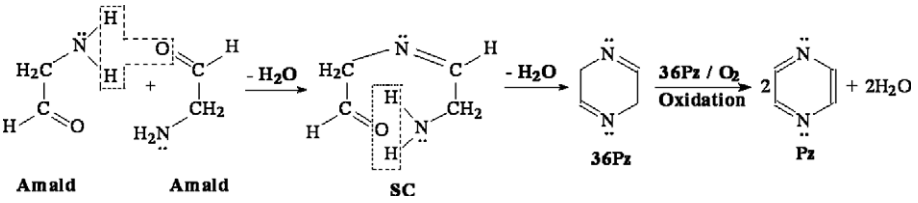


Fig. 3. Proposed mechanism for the self-condensation between amino acetaldehydes and oxidation of 3,6-dihydro pyrazine (**36Pz**) to 2,3,5,6-tetra-hydro pyrazine (**Pz**). *Abbreviations*: **Amald** = amino acetaldehyde (2-amino acetaldehyde or 2-amino ethanone-1); **SC** = intermediate self-condensation product.

of energy changes for different steps of a reaction, especially when it is a complex one, such as the Maillard reaction. Therefore, only general low energy structures, optimized at RB3LYP (Foresman & Frisch, 1996; Frisch & Foresman, 1998), of the compounds have been used in both of the gaseous and aqueous states to avoid complexities and to simplify the calculation (Shipar et al., submitted for publication). For all calculations, the 6-31G(*d*) polarized basis set (Foresman & Frisch, 1996; Frisch & Foresman, 1998) has been used. During optimization, all structural parameters, e.g. bond-lengths, bond-angles and dihedral angles, were considered as variables. The phrase "Stationary point found" in the geometry output confirmed that the ground state (Foresman & Frisch, 1996; Frisch & Foresman, 1998) was found. As many of the compounds in the proposed mechanisms (Figs. 1–3) can take stable cyclic forms, special care was taken during the optimization to avoid intramolecular cyclization (Shipar et al., submitted for publication). RB3LYP/6-31G(*d*) geometric parameters of **Gox** and **Gly** species (**UGly**, **PGly**, **DGly** and **GlyZ**) have been reported previously (Shipar et al., submitted for publication). 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^{o}), in the gaseous state and aqueous solution, respectively (Foresman & Frisch, 1996; Frisch & Foresman, 1998). Opt = *Z*-matrix and/or Freq = No Raman keywords have been used when necessary (Foresman & Frisch, 1996; Frisch & Foresman, 1998). By using RB3LYP/6-31G(*d*) and PCM/RB3LYP/6-31G(*d*) on the RB3LYP/6-31G(*d*) optimized structures, relevant electronic energies in the gaseous and aqueous states, respectively, have been calculated (Foresman & Frisch, 1996; Frisch & Foresman, 1998). The dielectric constant, $\varepsilon = 78.39$ has been used to represent aqueous solution (Frisch & Foresman, 1998; Foresman & Frisch, 1996). Relevant ZPE values have been added to the electronic energies to get the total electronic energies (E^{o}). Finally, electronic and free energy changes ($\Delta E^{o} = E^{o}_{\text{Product(s)}} - E^{o}_{\text{Reactant(s)}}$, and $\Delta G^{o} = G^{o}_{\text{Product(s)}} - G^{o}_{\text{Reactant(s)}}$, respectively) for different compounds in the proposed mechanisms (Figs. 1–3) 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

ΔG of a reaction indicates the spontaneity, whereas ΔE indicates the internal energy changes of the reaction at constant temperature and pressure. ΔG^{o} and ΔE^{o} for the formation of different compounds in the proposed mechanisms (Figs. 1–3) are presented in Tables 1 and 2, respectively, calculated by using **Hald** + **Gly** total electronic and free energies ($E^{o}_{\text{Hald}} + E^{o}_{\text{UGly/PGly/DGly/GlyZ}}$ and $G^{o}_{\text{Hald}} + G^{o}_{\text{UGly/PGly/DGly/GlyZ}}$, respectively (Shipar et al., submitted for publication)) as the standard in the equation $\Delta E^{o} = E^{o}_{\text{Product(s)}} - E^{o}_{\text{Reactant(s)}}$ and $\Delta G^{o} = G^{o}_{\text{Product(s)}} - G^{o}_{\text{Reactant(s)}}$, respectively. As mass balance of a reaction is related to the energy changes, the total mass balance of the reaction under different pH conditions (Figs. 1–3) have been maintained during the calculation of ΔG^{o} and ΔE^{o}. The main problem in balancing the total mass arises for protonation, deprotonation, and addition or elimination of OH^{-}. Therefore, the following ideas have been applied during balancing the total mass (Shipar et al., submitted for publication):

$$\underset{\text{Proton}}{H^{+}} + \underset{\text{water}}{H_2O} \rightleftarrows \underset{\text{hydroxonium ion}}{H_3O^{+}}$$

(protonation and deprotonation)

$$\underset{\text{Hydroxonium ion}}{H_3O^{+}} + \underset{\text{Hydroxide ion}}{OH^{-}} \rightleftarrows \underset{\text{water}}{2H_2O}$$

(addition and elimination of OH^{-})

According to ΔG^{o}, formation of all compounds in the proposed mechanisms (Figs. 1–3) is plausible. Therefore, **Hald** + **Gly** reaction is guessed to be more favourable for the production of **Pz**s than that of glyceraldehyde + **Gly** (Shipar, 2004) and dihydroxyacetone + **Gly** (Shipar, 2006) reactions. This can be taken as an explanation for higher activity of **Hald** in nonenzymatic browning than other carbonyl compounds as reported previously by (Hayashi & Namiki, 1986). It also reveals that **Gox**, formed in the early stage of **Hald** + **Gly** reaction (Shipar et al., submitted for publication), can instantaneously perform in the Strecker degradation (Figs. 1 and 2), self-condensation and oxidation (Fig. 3), and relevant **Pz**s can be produced.

Addition adducts of carbonyl and amino compounds are formed spontaneously in the Maillard reaction (Davídek et al., 1990; Eskin, 1990; Hodge, 1953; Macrane et al., 1993). Based on ΔG^{o} (Table 1), **Hald** + **DGly** reaction under basic conditions is the most favourable for

Table 1
ΔG^{o} (in kJ/mol) for different compounds presented in Figs. 1–3, calculated by using **Hald + Gly** total free energies ($G^{o}_{Hald} + G^{o}_{UGly/PGly/DGly/GlyZ}$ (Shipar et al., submitted for publication)) as the standard in the equation $\Delta G^{o} = G^{o}_{Product(s)} - G^{o}_{Reactant(s)}$

Compounds	Reactions							
	Hald + UGly		**Hald + PGly**		**Hald + DGly**		**Hald + GlyZ**	
	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous
Gox[a]	−356.6	−342.2	−355.7	−341.6	−356.8	−342.3	−356.0	−341.9
Goxadd	−385.1	−467.4	–	–	–	–	–	–
Goxadd(PGly)	–	–	−274.7	−883.6	–	–	–	–
Gox(DGly)	–	–	–	–	−420.1	−1040.5	–	–
Goxadd (DGly)	–	–	–	–	−611.9	−1110.0	–	–
Goxadd(GlyZ)	–	–	–	–	–	–	−331.4	−441.2
SB	−345.6	−436.4	–	–	–	–	–	–
SB(PGly)	–	–	−225.0	−764.4	–	–	–	–
SB(DGly)	–	–	–	–	−542.8	−1010.5	–	–
SB(GlyZ)	–	–	–	–	–	–	−509.5	−423.2
MIEne	−515.3	−510.6	–	–	–	–	–	–
MIEne(PGly)	–	–	−411.4	−880.3	–	–	–	–
MIEne(DGly)	–	–	–	–	−556.6	−1027.0	–	–
MIAce	−542.4	−552.4	–	–	−2158.6	−2162.4	−707.3	−557.0
MIAceN	−841.1	−1406.4	−414.0	−928.6	–	–	−1005.9	−1411.1
MIAceC	900.1	−1431.0	−473.1	−953.1	–	–	−1065.0	−1435.6
Glyald	−562.3	−611.9	−135.3	−134.1	−2178.5	−2222.0	−727.2	−616.5
Amald	−582.9	609.6	−155.8	−131.7	−2199.1	−2219.6	−747.7	−614.2
SC	−1036.0	−1067.3	−181.9	−111.7	−4268.4	−4287.5	−1365.7	−1076.6
36Pz	−1095.0	−1138.8	−240.8	−183.1	−4327.3	−4359.0	−1424.6	−1148.1
Pz	−1676.8	−1716.7	−822.7	−761.1	−4909.3	−4937.0	−2006.6	−1726.0

For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 1–3.

[a] Shipar et al. (submitted for publication).

Table 2
ΔE^{o} (in kJ/mol) for different compounds presented in Figs. 1–3, calculated by using **Hald + Gly** total electronic energies ($E^{o}_{Hald} + E^{o}_{UGly/PGly/DGly/GlyZ}$ (Shipar et al., submitted for publication)) as the standard in the equation $\Delta E^{o} = E^{o}_{Product(s)} - E^{o}_{Reactant(s)}$

Compounds	Reactions							
	Hald + UGly		**Hald + PGly**		**Hald + DGly**		**Hald + GlyZ**	
	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous
Gox[a]	−356.6	−342.2	−355.7	−341.6	−356.8	−342.3	−356.0	−341.9
Goxadd	−446.0	−528.2	–	–	–	–	–	–
Goxadd(PGly)	–	–	−341.8	−391.5	–	–	–	–
Gox(DGly)	–	–	–	–	−375.4	−995.8	–	–
Goxadd (DGly)	–	–	–	–	−559.2	−1057.1	–	–
Goxadd(GlyZ)	–	–	–	–	–	–	−402.3	−3164.9
SB	−313.0	−403.9	–	–	–	–	–	–
SB(PGly)	–	–	−210.3	−190.6	–	–	–	–
SB(DGly)	–	–	–	–	−411.6	−879.3	–	–
SB(GlyZ)	–	–	–	–	–	–	−502.7	−4470.6
MIEne	−412.4	−411.3	–	–	–	–	–	–
MIEne(PGly)	–	–	−306.8	−220.1	–	–	–	–
MIEne(DGly)	–	–	–	–	−1007.4	−809.2	–	–
MIAce	−433.3	−447.0	–	–	−1932.9	−1940.4	−595.7	−4503.3
MIAceN	−738.8	−1307.9	−309.8	−268.9	–	–	−901.1	−6765.4
MIAceC	−798.8	−1333.3	−369.8	−294.4	–	–	−961.2	−6790.9
Glyald	−534.6	−587.8	−105.6	451.1	−2034.1	−2081.2	−697.0	−3242.9
Amald	−466.1	−491.1	−37.1	547.8	−1965.6	−1984.5	−628.5	−3146.2
SC	−823.3	−851.3	34.6	1226.5	−3822.4	−3838.1	−1148.0	−7562.7
36Pz	−810.7	−851.3	47.2	1226.6	−3809.7	−3838.07	−1135.4	−8963.9
Pz	−1356.6	−1393.2	−498.7	684.6	−4355.7	−4380.0	−1681.4	−10907.1

For abbreviations and details of the compounds, see the captions and mechanisms of Figs. 1–3.

[a] Shipar et al. (submitted for publication).

forming the addition compound 2-deprotonated glycino-2-hydroxy acetaldehyde or 2-deprotonated glycino-2-hydroxy ethanone-1 [**Goxadd(DGly)**; Fig. 2] in both of the gaseous state and aqueous solution, and the aqueous solution is more feasible than that of the gaseous state. In the gaseous state, **Hald + UGly** reaction under neutral

conditions and **Hald + GlyZ** reaction at the isoelectric point of glycine are the second and third most feasible for the formation of the addition compounds 2-glycino-2-hydroxy acetaldehyde or 2-glycino-2-hydroxy ethanone-1 (**Goxadd**; Fig. 1) and **Goxadd(GlyZ)** (Fig. 2), respectively (Table 1). **Hald + PGly** reaction under acidic conditions is the least feasible for forming the addition compound 2-protonated glycino-2-hydroxy acetaldehyde or 2-protonated glycino-2-hydroxy ethanone-1 [**Goxadd(PGly)**; Fig. 1] in the gaseous state (Table 1). On the other hand, **Hald + PGly** and **Hald + UGly** reactions are the second and third most favourable, and **Hald + GlyZ** reaction is the least favourable for producing the addition compounds in aqueous solution (Table 1). In **Hald + DGly** reaction, formation of the ionic addition adduct **Gox(DGly)** (Fig. 2) is less favourable than the formation of **Goxadd(DGly)** in both of the gaseous state and aqueous solution (Table 1). Based on ΔE^{o} (Table 2), all addition compounds [**Goxadd**, **Goxadd(PGly)**, **Goxadd(DGly)** and **Goxadd(GlyZ)**] are electronically more stable in aqueous solution than that of the gaseous state, and in both of the gaseous state and aqueous solution, **Goxadd(DGly)** is electronically more stable than **Goxadd**, **Goxadd(PGly)** and **Goxadd(GlyZ)**. **Gox(DGly)** is electronically less stable than **Goxadd(DGly)** in both of the gaseous state and aqueous solution (Table 2). ΔG^{o} and ΔE^{o} for the production of the addition compound and the Schiff base under basic conditions are much larger in aqueous solution than that of the others. Therefore, production of these species under basic conditions would be much easier than that of the others. Hence, these species could easily be evaluated and detected experimentally in the reaction.

The Schiff bases are one of the most common intermediates in the Maillard reaction, which can undergo further reactions to form more intermediates that are more reactive (Davídek et al., 1990; Eskin, 1990; Hodge, 1953; Macrane et al., 1993; Nyhammar, Olsson, & Pernemalm, 1983). **Hald + DGly** reaction is the most favourable for the formation of the Schiff base 2-deprotonated glycino acetaldehyde or 2-deprotonated glycino ethanone-1 [**SB(DGly)**] in both of the gaseous state and aqueous solution, and the aqueous solution is more feasible than that of the gaseous state (Table 1). In the gaseous state, **Hald + GlyZ** and **Hald + UGly** reactions are the second and third most favourable for producing the Schiff bases, **SB(GlyZ)** [Schiff base of **Gox** and **GlyZ**] and **SB** (2-glycino acetaldehyde or 2-glycino ethanone-1), respectively, whereas **Hald + PGly** reaction is the least favourable for producing the Schiff base 2-protonated glycino acetaldehyde or 2-protonated glycino ethanone-1 [**SB(PGly)**] (Table 1). In aqueous solution, **Hald + PGly**, **Hald + UGly** reactions are the second and third most favourable for producing the Schiff bases (Table 1). **Hald + GlyZ** reaction is the least feasible for producing the Schiff base in aqueous solution (Table 1). The Schiff bases, **SB**, **SB(DGly)** and **SB(GlyZ)** are electronically more stable in aqueous solution, whereas **SB(PGly)** is electronically more stable in the gaseous state.

Except 2-methylimino acetone or 2-methylimino ethanone-1 (**MIAce**) in **Hald + GlyZ** reaction, formation of 1-methylimino-2-hydroxy ethene-1 (**MIEne**), ionic adducts of **MIEne**, i.e. **MIEne(PGly)** and **MIEne(DGly)**, **MIAce**, **MIAceN** (a nitro-cationic adduct of **MIAce**) and **MIAceC** (a carbo-cationic adduct of **MIAce**) under all pH conditions is more feasible in aqueous solution than the gaseous state reaction (Table 1). The gaseous state **Hald + GlyZ** reaction is more favourable for the formation of **MIAce** than that of the aqueous solution (Table 1). Formation of **MIEne** and its adducts, **MIEne(PGly)** and **MIEne(DGly)**, is assumed more feasible in aqueous solution than the gaseous state reactions. In both of the gaseous state and aqueous solution, **Hald + DGly** reaction is more favourable for producing **MIAce** than **Hald + UGly** and **Hald + GlyZ** reactions (Table 1). In producing **MIAceN** and **MIAceC**, **Hald + GlyZ** reaction is more feasible than **Hald + UGly** and **Hald + PGly** reactions in both of the gaseous state and aqueous solution (Table 1). **MIEne**, **MIEne(PGly)** and **MIEne(DGly)** are found electronically be more stable in the gaseous state than aqueous solution (Table 2). Except **MIAceN** and **MIAceC** in **Hald + PGly** reaction, **MIAce**, **MIAceN** and **MIAceC** are electronically more stable in aqueous solution than the gaseous state (Table 2). Both **MIAceN** and **MIAceC** are electronically more stable in **Hald + PGly** gaseous state reaction than that of the aqueous solution (Table 2). Production of **MIEne**, **MIEne(PGly)**, **MIEne(DGly)**, **MIAce**, **MIAceN** and **MIAceC** in **Hald + Gly** reaction has not been studied at all, and therefore, information on these species in the reaction is quite insufficient.

Hald + DGly reaction is the most favourable for the formation of 2-glycino acetaldehyde or 2-glycino ethanone-1 (**Glyald**), 2-amino acetaldehyde or 2-amino ethanone-1 (**Amald**), intermediate self-condensation compound (**SC**) and **Pz**s (**36Pz** [$C_4N_2H_6$] and **Pz** [$C_4N_2H_4$]), and the reaction in aqueous solution is more feasible than that of the gaseous state (Table 1). Effect of pH in the Maillard reaction is not clear-cut or obvious at all. However, the present evaluation is consistent with the prior findings that the rate of browning is usually increased at high pH or under basic conditions due to the availability of carbonyl compounds in their reducing forms (Ames, 1990; Bell, 1997; Davídek et al., 1990; Eskin, 1990; Lea & Hannan, 1949; Macrane et al., 1993; Shipar, 2004, 2006). ΔG^{o} and ΔE^{o} for the formation of **Glyald**, **Amald**, **SC**, **36Pz** and **Pz** under basic conditions are much larger than that of the others. Therefore, under basic conditions, these species could form much easily than that of the others. Hence, these species would easily be evaluated and detected experimentally in the reaction under this condition.

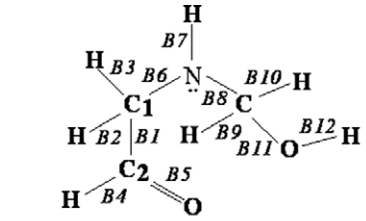
For the formation of **Glyald**, **Amald**, **SC** and **Pz**s, **Hald + GlyZ** reaction is supposed to be the second most favourable, and the gaseous state reaction is more feasible than that of the aqueous solution (Table 1). As **Hald + GlyZ** reaction has been reported not to be favourable for the formation of **Gox** in the early stage (Shipar et al., submitted for

publication), production of **Pz**s under this condition may be hindered. However, profound information on the Maillard reaction under this condition is still not available.

Hald + **UGly** reaction is found to be the third most favourable for the formation of **Sc**, **Amald**, **Glyald** and **Pz**s, and similar to **Hald** + **DGly** reaction, the aqueous solution is more feasible than that of the gaseous state (Table 1). Sufficient information on the Maillard reaction under this condition is also inadequate.

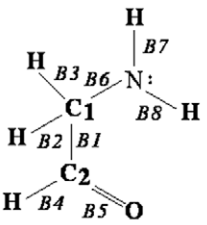
Hald + **PGly** reaction is the least favourable for the formation of **Glyald**, **Amald**, **SC** and **Pz**s (Table 1). **Hald** + **PGly** reaction has been reported as less favourable for the formation of **Gox** in the early stage (Shipar et al., submitted for publication), and therefore, production of **Pz**s under this condition may be mired. It is in agreement with the previous report that acidic or protonated forms of amino groups of amino compounds are not favourable for the Maillard reaction (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). Similar to **Hald** + **GlyZ** reaction, the gaseous state **Hald** + **PGly** reaction is more favourable than that of the aqueous solution for producing **Glyald**, **Amald**, **SC** and **Pz**s (Table 1). RB3LYP/6-31G(*d*) geometric parameters of **Glyald** and **Amald** are presented in Fig. 4, and **36Pz** and **Pz** are in Fig. 5.

Amald, formed through the Strecker degradation of **Gox** and **Gly** species (**UGly**, **PGly**, **DGly** and **GlyZ** [Figs. 1–4]), is the most likely precursor of the pyrazine ring. It may possible that **Glyald** could follow some other mechanisms to produce the pyrazine ring. Sufficient experimental data on these species are still not available. However, under all pH conditions, formation of **Amald** is more feasible in the gaseous state reaction, whereas **Glyald** in aqueous solution (Table 1). In **Hald** + **UGly** and **Hald** + **DGly** reactions, both **Amald** and **Glyald** are electronically more stable in aqueous solution than that of the gaseous state (Table 2). Both **Amald** and **Glyald** are electronically more stable in the gaseous state than that of the aqueous **Hald** + **PGly** reaction (Table 2). **Glyald** is electronically more stable in the gaseous state **Hald** + **GlyZ** reaction, whereas **Amald** is electronically more stable in aqueous **Hald** + **GlyZ** reaction (Table 2). It is remarkable that different compounds formed in the aqueous solution of



B1 = 1.5222 Å, *B2* = 1.1003 Å, *B3* = 1.1024 Å, *B4* = 1.115 Å, *B5* = 1.211 Å, *B6* = 1.4486 Å, *B7* = 1.0191 Å, *B8* = 1.4594 Å, *B9* = 1.1038 Å, *B10* = 1.097 Å, *B11* = 1.4076 Å, *B12* = 0.9721 Å, C_1-C_2-O = 124°, C_1-C_2-H = 115°, C_1-N-C = 115.6°, N-C-O = 110°, C-O-H = 105.8°, C_2-C_1-N-C = -72.5°, C_1-N-C-O = -165.4°, N-C-O-H = 48.3°.

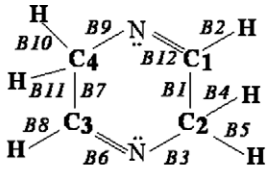
Glyald



B1 = 1.5207 Å, *B2* = 1.1009 Å, *B3* = 1.101 Å, *B4* = 1.1149 Å, *B5* = 1.2115 Å, *B6* = 1.4527 Å, *B7* = 1.0194 Å, *B8* = 1.0194 Å, C_1-C_2-O = 123.8°, C_1-C_2-H = 115.2°, C_1-N-H = 108.79°, C_1-N-H = 108.77°, C_2-C_1-N-H = 56.68°, C_2-C_1-N-H = -56.75°.

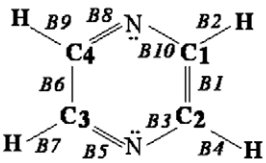
Amald

Fig. 4. RB3LYP/6-31G(*d*) geometric parameters of glycino acetaldehyde (**Glyald**) and amino acetaldehyde (**Amald**).



B1 = 1.5111 Å, *B2* = 1.095 Å, *B3* = 1.4636 Å, *B4* = 1.1015 Å, *B5* = 1.098 Å, *B6* = 1.272 Å, *B7* = 1.5112 Å, *B8* = 1.095 Å, *B9* = 1.4635 Å, *B10* = 1.0979 Å, *B11* = 1.1016 Å, *B12* = 1.272 Å, N-C_1-C_2 = 125.7°, N-C_1-H = 117.3°, C_1-C_2-N = 114.7°, C_2-N-C_3 = 116.23°, N-C_3-H = 117.3°, N-C_3-C_4 = 125.7°, C_3-C_4-N = 114.7°, N-C_1-C_2-N = 20.67°, N-C_4-C_3-N = 20.68°.

36Pz



B1 = 1.3971 Å, *B2* = 1.0884 Å, *B3* = 1.3378 Å, *B4* = 1.0884 Å, *B5* = 1.3379 Å, *B6* = 1.3969 Å, *B7* = 1.0884 Å, *B8* = 1.3379 Å, *B9* = 1.0884 Å, *B10* = 1.3378 Å, N-C_1-C_2 = 122.1°, N-C_1-H = 117°, C_1-C_2-N = 122.1°, C_1-C_2-H = 120.9°, C_2-N-C_3 = 115.8°, N-C_3-H = 117°, N-C_3-C_4 = 122.1°, C_3-C_4-H = 120.9°, C_3-C_4-N = 122.1°, N-C_1-C_2-N = 0°, N-C_4-C_3-N = 0°.

Pz

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

Hald + GlyZ reaction are electronically highly stable (Table 2). Therefore, the reaction under this condition may posses an important role for the production of **Pz**s.

Air or oxygen is generally required during the production of Maillard flavours and aromas (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). In both of the gaseous state and aqueous solution, oxidation plays an important role during the production of **Pz** from **36Pz** (Table 1). Hence, presence of air or oxygen with **Gox** is necessary for the production of **Pz** from **36Pz** in **Hald + Gly** reaction under all pH conditions.

According to the total mass balance, four molecules of H_2O are required with **Gox** for the production of **Pz**s under each of the neutral (**Hald + UGly** reaction), acidic (**Hald + PGly** reaction) and basic (**Hald + DGly** reaction) conditions, whereas six molecules are required at the isoelectric point of glycine (**Hald + GlyZ** reaction). During the formation of **36Pz**, total 10 molecules of H_2O are produced as by-product than the initiation step of **Hald + UGly**, **Hald + PGly** and **Hald + DGly** reactions (Shipar et al., submitted for publication), whereas total twelve molecules are produced in **Hald + GlyZ** reaction. On the other hand, for the production of **Pz**, total twelve molecules of H_2O are found to be produced as by-product than the initiation step of **Hald + UGly**, **Hald + PGly** and **Hald + DGly** reactions (Shipar et al., submitted for publication), whereas total fourteen molecules are produced in **Hald + GlyZ** reaction. It is in agreement with previous statements that water is necessary, and is a by-product, for the production of melanoidins in the Maillard reaction (Ames, 1990; Davídek et al., 1990; Eskin, 1990; Labuza & Saltmarch, 1981; Lea & Hannan, 1949; Macrane et al., 1993; Nursten, 1986).

4. Conclusions

From the present theoretical calculations, possible order for the formation of **Pz**s (**36Pz** and **Pz**) at the standard state is found as **Hald + DGly** aqueous > **Hald + DGly** gaseous > **Hald + GlyZ** gaseous > **Hald + GlyZ** aqueous > **Hald + UGly** aqueous > **Hald + UGly** gaseous > **Hald + PGly** gaseous > **Hald + PGly** aqueous state reactions. The reaction under basic conditions is the most suitable for following the general Hodge-scheme (Hodge, 1953). The Maillard reaction mainly takes place in foods as well as in the human body (Davídek et al., 1990; Eskin, 1990; Ledl & Schleicher, 1990; Macrane et al., 1993; Meade et al., 2003; Reber et al., 2002). This finding is, therefore, important and much contract with the previous reports. Experimental evaluation and detection of the related intermediates is difficult as they readily undergo further reactions, and the final products in the Maillard reaction have a tendency to produce complex mixtures. However, the result would be helpful in performing experimental studies to find out proper mechanisms for the reaction in foods and other systems, such as in the human body. The global minima, minima, maxima and transition states of different compounds on the potential energy surfaces are also necessary to find out. It will be useful to obtain information about the error in ΔE^{o} and ΔG^{o} of different compounds caused by using conformations other than the ones at the global minima. In order to fulfill this intention, extensive theoretical studies on the potential energy surfaces of different compounds in the reaction are required. However, the computational results can generally be varied from 10% to 15% with experiments (Hehre, Radom, Schleyer, & Pople, 1986; Young, 2001). Adequate data are still not available, and therefore, extensive exertions are required to find out the controlling techniques of the Maillard reactions, leading to the production of desirable yields.

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