

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

Abraham F. Jalbout^{a,*}, M.D. Abul Haider Shipar^{b,*}, B. Trzaskowski^a, Ludwik Adamowicz^a

^a NASA Astrobiology Institute, Department of Chemistry, The University of Arizona, Tucson, AZ 85721, USA

^b Department of Information and Image Sciences, Faculty of Engineering, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

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Abstract

Density functional theory (DFT) computations at the standard state on the proposed mechanisms have revealed that glyoxal (Gox) is one of the most possible intermediates in the hydroxyacetaldehyde (Hald) and glycine nonenzymatic browning Maillard reaction under different pH conditions. By following the total mass balance, the gaseous state reaction has been found as more feasible for the formation of Gox than that of the aqueous solution. Hald + deprotonated glycine reaction under basic condition and Hald + unprotonated glycine reaction under neutral condition have been supposed to be more favorable for the production of Gox than Hald + protonated glycine reaction under acidic condition and Hald + glycine zwitterion reaction at the isoelectric point of glycine. Oxidation of Hald to Gox has been found as more plausible in the gaseous state than the aqueous solution. Oxygen has been found as necessary for the production of Gox from Hald. At the standard state, DFT calculations on the proposed mechanisms have evaluated that unprotonated and deprotonated glycine and glycine zwitterion are feasible for liberating NH₃, whereas protonated glycine has been found as unfeasible. DFT computations at the standard state on the proposed mechanisms have also revealed that the gaseous state Hald + NH₃ reaction is more feasible for the formation of Fald than that of the aqueous solution. Water, which is a by-product, has found as necessary for the initiation of both of Hald + glycine and Hald + NH₃ reactions.

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1. Introduction

Hydroxyacetaldehyde (Hald) or glycolaldehyde (C₂H₄O₂) is an important C₂-sugar fragmentation product in nonenzymatic browning or the so-called Maillard reaction (Hayashi & Namiki, 1986; Hodge, 1953; Maillard, 1912; Namiki & Hayashi, 1983; Tressl, Nittka, & Kersten, 1995). In general, Hald is produced in the early stage of the Maillard reaction, and especially, in the aqueous systems (Hayashi & Namiki, 1986; Namiki & Hayashi, 1983; Wee-

nen, De Valois, & Vonk, 1994). By using electron spin resonance spectroscopy, generation of Hald in the early stage of the Maillard reaction has been evaluated (Namiki & Hayashi, 1983). Weenen et al. (1994) reported that Hald is produced as a C₂-fragmentation product from 1- and 3-deoxyosone intermediates through retroaldol cleavage during the formation of pyrazines from hexoses and asparagines. Computational studies on glyceraldehyde (Gald) and glycine (Gly) Maillard reaction revealed that formation of Hald from Gald is favorable in the aqueous state, and not in the gaseous state (Shipar, 2004a). Computational studies on dihydroxyacetone (DHA) and Gly Maillard reaction revealed that formation of Hald from dihydroxyacetone is more favorable in the aqueous state than that of the gaseous state (Shipar, 2006). Due to high

* Corresponding authors. Present address: Institute of Chemistry, National Autonomous University of Mexico, Mexico City. Tel.: +1 520 621 6761 (A.F. Jalbout).

E-mail address: ajalbout@u.arizona.edu (A.F. Jalbout), Shipar7@yahoo.com (M.D.A.H. Shipar).

reactivity in free radical formation, C2-sugar fragmentation products, such as, Hald, play an important role in the Maillard reaction (Weenen et al., 1994). Free radicals can be formed from glycosylamine without the formation of the Amadori rearrangement products (ARPs), and intermediates of the reaction include highly reactive two-carbon fission products of the sugar (Hayashi & Namiki, 1986; Namiki & Hayashi, 1983). C2-fragmentation products, e.g. Hald, can also be formed from ARPs in the intermediate stage of the reaction (Davídek, Velíšek, & Pokorný, 1990; Macrane, Robinson, & Saadler, 1993). Hald exhibits much higher browning rates than glyceraldehyde, glucose, fructose, xylose, glyoxal and methyl glyoxal (Hayashi & Namiki, 1986). Hald is not a reducing sugar. However, it contains carbonyl and hydroxyl groups, and therefore, structurally it is similar to sugars. It can lead to the formation of the Maillard products, collectively known as melanoidines, through nonenzymatic browning (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). Thus, the rate of browning in the sugar-amino compound reaction can be enhanced. Though high reactivity of Hald in the Maillard reaction has been reported (Hayashi & Namiki, 1986; Namiki & Hayashi, 1983), mechanism for the formation of melanoidines has not been well studied. It should be counted that the Maillard reaction can follow various pathways, and various melanoidines with different characteristics can be produced through the formation of different intermediates (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). Moreover, production of the intermediates and final products can be varied with time and temperatures (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). Studies on model systems showed that an increase in temperature and/or time of heating results in the increase in color development, the carbon-to-nitrogen ratio and the degree of unsaturation and the chemical aromaticity. Thermal treatments of carbohydrates and L-alanine at 95 °C have revealed that color development can be occurred through the production of dialkylpyrazinium radical cation, prior to which, glyoxal is formed as an early product (Hofmann, Bors, & Stettmaier, 1999). During storage and processing of foods, the reactions take place at elevated temperatures as well as at normal or reduced temperatures, even at 0 °C (Davídek et al., 1990; Macrane et al., 1993). With increase of temperature by 10 °C, the rate of the reaction increases 2–3 times (Ho, 1996; Parliament, 1989). At higher temperatures and/or longer time, however, other reactions, such as formation of mutagenic products can take place, which do not occur at normal temperatures and/or short time (Davídek et al., 1990; Macrane et al., 1993). At even greater temperatures, degradation of carbohydrates and amino compounds can be occurred (Macrane et al., 1993; Nyhammar, Grivas, Olsson, & Jagerstad, 1986; Nyhammar, Olsson, & Pernemalm, 1983; Wong & Shibamoto, 1996). Previous studies were related mainly to higher temperatures, and generally overlooked the role of the Maillard reaction at lower temperatures, such as at the standard state, at which the reaction can

mainly takes place in stored foods. However, it is generally agreed that the rate of browning reaction at lower temperatures is very low, and therefore, difficult to follow the reaction for precise information. Due to much more complexities, conducting experiments and analysing the intermediate and final product mixtures for accurate information, is also complicated. Computational model chemistry can be applied on such a complex reaction to obtain useful information, which will be helpful to understand and establish proper reaction mechanism. Previous studies were also linked mostly 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 Hald. In the present study, by considering the formation of glyoxal (Gox) as one of the possible products, mechanisms for the early stage of the nonenzymatic Maillard browning reaction between Hald and Gly under different pH conditions are proposed and described, followed usually the Hodge-scheme (Hodge, 1953). By following the total mass balance of the reaction, density functional computations at the standard state have been performed to evaluate the possibility of the formation of different compounds in the proposed mechanisms through the estimation of the Gibb's free energy changes (ΔG°). Electronic energy changes (ΔE°) have also been evaluated to observe the internal energy changes during the reaction. Possibility of the oxidation of Hald to Gox ($\text{Hald} + \text{O}_2 \rightarrow \text{Gox} + \text{H}_2\text{O}$) has been evaluated by following the total mass balance of the reaction. Dipole moments and heats of formation of different compounds have also been estimated.

In Hald, the H atoms are electrophilic, and because of only one hydroxyl group, which is a nucleophile, electron flow to the carbonyl carbon is lower than that of glyceraldehyde, glucose, etc., which contain more than one hydroxyl groups. As a result, positive charge on the carbonyl carbon of Hald might be higher than that of other carbonyl compounds, and therefore, carbonyl carbon of Hald might be more suitable for the nucleophilic attack. The nucleophilic amino group of amino compound with the lone pair electron on the nitrogen can readily attack on the electron deficient carbonyl carbon of Hald to form the addition compound, hydroxyacetaldehydeamine or glycolaldehydeamine, which can form the highly reactive Schiff base, hydroxyacetaldehydeimine or glycolaldehydeimine, by the elimination of water. It can undergo further reactions to produce highly reactive compounds, such as the dicarbonyl compound glyoxal (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). Further reactions can take place successively, and more browning compounds can be produced. Therefore, the overall rate of browning can be increased significantly. By using PCILO semiempirical quantum-chemical method, Fedoronko, Temkovic, Konigstein, Kovacik, and Tvaroska (1980) have been studied some

electronic structures of Hald. By using ab initio quantum mechanical calculations up to MP4(SDQ)/6-31+G**//HF/6-31+G*, Peräkylä (1997) has been studied some conformations of Hald, and the solvent effect has been observed by using the polarisable continuum method (PCM). However, information on Hald is still not sufficient, and due to important role in the Maillard reaction, more information on Hald is still required.

Unionized or unprotonated glycine (UGly, $\text{H}_2\text{N}-\text{CH}_2-\text{CO}_2\text{H}$) becomes the dominant species in the gaseous state,

and can exist at a very low concentration in neutral (pH 7) aqueous solution (Holum, 1996; Harrold, 1991). In acidic solution, Gly is completely protonated ($\text{H}_3\text{N}^+-\text{CH}_2-$

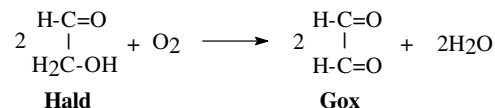


Fig. 3. Oxidation of hydroxyacetaldehyde (Hald) to glyoxal (Gox).

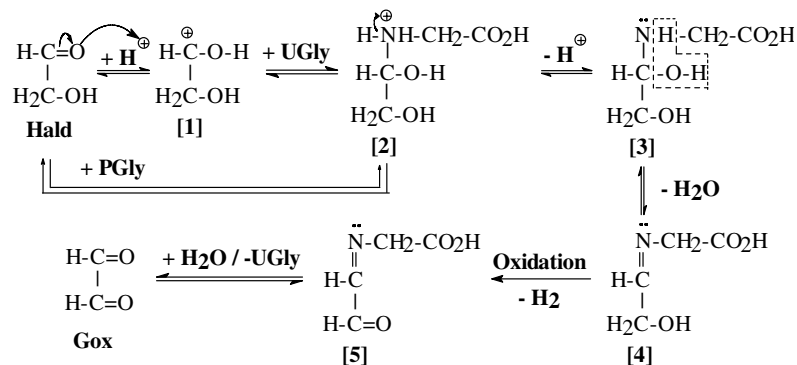


Fig. 1. Proposed mechanisms for the formation of glyoxal (Gox) in Hald + UGly and Hald + PGly Maillard reactions. *Abbreviations:* Hald, hydroxyacetaldehyde; UGly, unionized or unprotonated glycine; PGly, protonated glycine; Gox, glyoxal. *Numerical abbreviations:* 1, protonated form of Hald; 2, ionic adduct of glycolglycine (1-protonated glycino-1,2-dihydroxy ethane or 1-protonated glycino-1-hydroxy ethanol); 3, glycolglycine addition compound (1-glycino-1,2-dihydroxy ethane or 1-glycino-1-hydroxy ethanol); 4, Schiff base of glycolglycine (1-glycino-2-hydroxy ethane or 1-glycino ethanol); 5, glyoxal monoglycine. In Hald + PGly reaction, the eliminated UGly is instantly protonated to PGly, and mass–energy balance is maintained accordingly during the calculation of ΔG° and ΔE° .

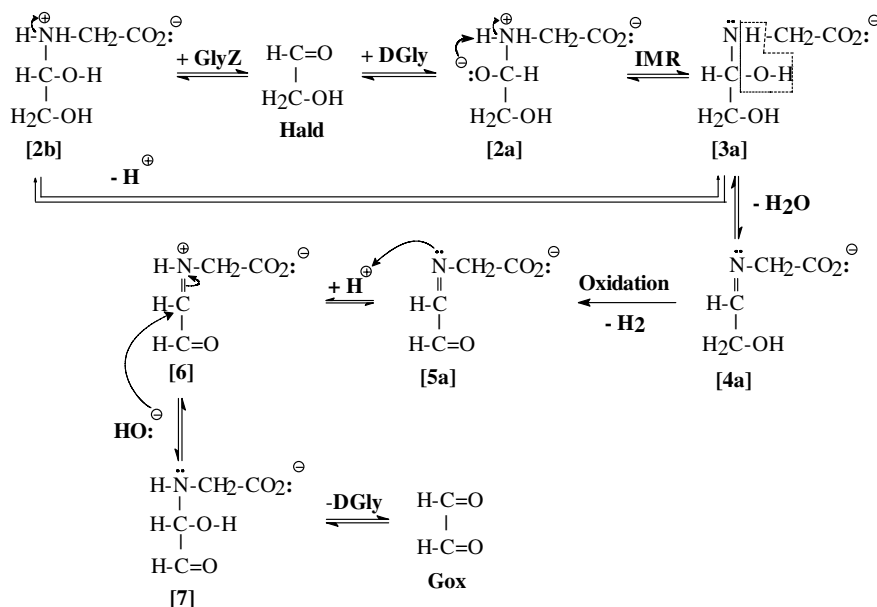


Fig. 2. Proposed mechanisms for the formation of glyoxal (Gox) in Hald + DGly and Hald + GlyZ Maillard reactions. *Abbreviations:* DGly, deprotonated glycine; GlyZ, glycine zwitterion; IMR, intramolecular rearrangement. *Numerical abbreviations:* 2a, ionic addition adduct of Hald and DGly; 2b, ionic addition adduct of Hald and GlyZ; 3a, glycol-deprotonated glycine addition compound (1-deprotonated glycino-1,2-dihydroxy ethane or 2-deprotonated glycino-2-hydroxy ethanol); 4a, Schiff base of glycol-deprotonated glycine (1-deprotonated glycino-2-hydroxy ethane or 1-deprotonated glycino ethanol); 5a, glyoxal mono-deprotonated glycine (2-deprotonated glycino acetaldehyde); 6, an ionic adduct of 5a; 7, 2-deprotonated glycino-2-hydroxy acetaldehyde. For other abbreviations, see the caption of Fig. 1. In Hald + GlyZ reaction, the eliminated DGly is instantly protonated to GlyZ, and mass–energy balance is maintained accordingly during the calculation of ΔG° and ΔE° .

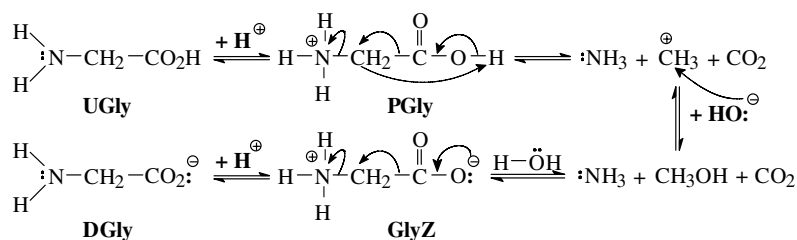


Fig. 4. Proposed mechanisms for the formation of ammonia (NH_3) from glycine (Gly) species. For abbreviations, see the captions of Figs. 1 and 2.

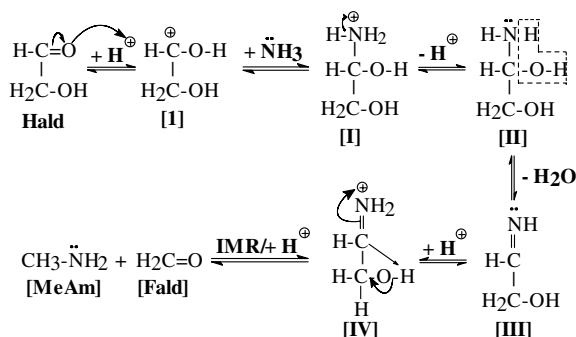


Fig. 5. Proposed mechanism for the reaction between hydroxyacetaldehyde (Hald) and ammonia (NH_3). *Abbreviations:* I, ionic addition adduct of glycolamine; II, glycolamine addition compound (1-amino-1,2-dihydroxy ethane or 1-amino-1-hydroxy ethanol); III, Schiff base of glycolamine (1-imino-2-hydroxy ethane or 1-imino ethanol); IV, an ionic adduct of the Schiff base of glycolamine; Fald, formaldehyde; MeAm, methylamine. For other abbreviations, see the captions of Figs. 1 and 2.

CO_2H) and exists as the conjugated acid (Holum, 1996; Harrold, 1991). Hence, under acidic conditions, e.g. $\text{pH} < 5.5$, protonated glycine (PGly) becomes the dominant species. Production of basic amino groups is facilitated by the alkaline medium, and therefore, deprotonated glycine (DGly, $\text{H}_2\text{N}-\text{CH}_2-\text{CO}_2^-$) becomes the dominant species under basic conditions ($\text{pH} > 8$) [Eskin, 1990]. Glycine zwitterion (GlyZ, $\text{H}_3\text{N}^+-\text{CH}_2-\text{CO}_2^-$) becomes the dominant species at the isoelectric point of Gly ($I = \text{pH} \approx 6$) (Holum, 1996; Harrold, 1991; Macrane et al., 1993). Under these circumstances, proposed mechanisms for Hald + UGly, Hald + PGly, Hald + DGly and Hald + GlyZ reactions are presented in Figs. 1 and 2, respectively. During the formation of Gox in Hald + PGly and Hald + GlyZ reactions (Figs. 1 and 2), the eliminated UGly and DGly can instantly be protonated to PGly and GlyZ, respectively, and the total mass balance has been maintained during the calculation of ΔG° and ΔE° .

Additionally, oxidation of Hald to Gox may take place in the system. Proposed mechanism for the oxidation of Hald to Gox is presented in Fig. 3.

Furthermore, Hald can perform in further reactions with ammonia (NH_3), liberated from amino compounds, such as glycine (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). However, sufficient information on this point is still not available. Mechanisms for the production of NH_3 from Gly species, and further reactions of Hald with

NH_3 , are proposed and presented in Figs. 4 and 5, respectively.

2. Methodology

At the standard state, all compounds in the proposed mechanisms (Figs. 1–5) have been studied in their gaseous and aqueous phases by using Gaussian 98 program (Becke, 1992a, 1992b, 1993, 1996; Foresman & Frisch, 1996; Frisch & Foresman, 1998; Frisch et al., 2001; Hehre, Radom, Schleyer, & Pople, 1986; Larid, Ross, & Ziegler, 1996; Miertus & Tomasi, 1982; Miertus, Scrocco, & Tomasi, 1981; Salahub et al., 1991; Springborg, 1995; Young, 2001). As all compounds in the proposed mechanisms (Figs. 1–5) can have many conformations in both of the gaseous and aqueous states, 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, only general optimized structures of the compounds at a specific method (RB3LYP) (Becke, 1992a, 1992b, 1993, 1996; Foresman & Frisch, 1996; Frisch & Foresman, 1998; Hehre et al., 1986) have been used in both of the gaseous and aqueous states to avoid complexities and simplify the calculation (Shipar, 2004a, 2006). 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). Moreover, many of the compounds in the proposed mechanisms (Figs. 1–5) can have their stable cyclic forms, and therefore, especial care has been taken during the optimization to avoid the possible intramolecular cyclization of the compounds (Shipar, 2004a, 2006). 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 states, 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 states 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, $\epsilon = 78.39$ 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, 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. 1–5) 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. Relevant dipole moments (μ , in Debye) of different compounds in the gaseous and aqueous states have been obtained from the single point energy calculations on the RB3LYP/6-31G(d) optimized structures at RB3LYP/6-31G(d) and PCM/RB3LYP/6-31G(d), respectively (Foresman & Frisch, 1996; Frisch & Foresman, 1998). Relevant heats of formation (ΔH_f°) of different compounds have been obtained by performing AM1 semi-empirical calculations

(Foresman & Frisch, 1996; Frisch & Foresman, 1998) on the RB3LYP/6-31G(d) optimized structures.

3. Results and discussion

At constant temperatures and pressures, ΔE and ΔG of a reaction provide the general prediction of the internal energy changes and spontaneity of the reaction, respectively. ΔG° for the formation of different compounds in the proposed mechanisms for Hald + Gly reaction under different pH conditions (Figs. 1 and 2) are presented in Table 1, calculated by using Hald + Gly total free energies ($G^\circ_{\text{Hald}} + G^\circ_{\text{UGly/Pgly/DGly/GlyZ}}$) as the standard in the equation $\Delta G^\circ = G^\circ_{\text{Product(s)}} - G^\circ_{\text{Reactant(s)}}$. Table 2 represents ΔE° of different compounds in the proposed mechanisms (Figs. 1 and 2), obtained by using Hald + Gly total electronic energies ($E^\circ_{\text{Hald}} + E^\circ_{\text{UGly/Pgly/DGly/GlyZ}}$) as the standard in the equation $\Delta E^\circ = E^\circ_{\text{Product(s)}} - E^\circ_{\text{Reactant(s)}}$. Values of μ and ΔH_f° of different compounds are presented in Table 3. Table 4 represents ΔG° and ΔE° for the formation of NH_3 from Gly species. ΔG° [calculated by using Hald + NH_3 total free energies ($G^\circ_{\text{Hald}} + G^\circ_{\text{NH}_3}$)] as the standard in the equation $\Delta G^\circ = G^\circ_{\text{Product(s)}} - G^\circ_{\text{Reactant(s)}}$, ΔE°

Table 1
 ΔG° (kJ/mol) for different compounds presented in Figs. 1 and 2

Reactions → Compounds ↓	Hald + UGly		Hald + PGly		Hald + DGly		Hald + GlyZ	
	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous
1	-104.3	-685.84	-	-	-	-	-	-
2	-352.7	-941.7	74.4	-463.8	-	-	-	-
2a	-	-	-	-	-12.4	-622.3	-	-
2b	-	-	-	-	-	-	126.6	-16.3
3	97.4	-10.1	524.5	467.7	-	-	-	-
3a	-	-	-	-	-23.7	-596.0	1427.7	1009.5
4	116.2	8.4	543.3	486.3	-	-	-	-
4a	-	-	-	-	0.03	-583.4	1451.4	1022.1
5	-341.9	-422.6	85.1	55.2	-	-	-	-
5a	-	-	-	-	-550.0	-1017.7	901.3	587.7
6	-	-	-	-	-1960.8	-2028.2	509.5	-422.7
7	-	-	-	-	-525.8	-1072.2	925.6	533.2
Gox	-396.9	-383.3	-396.1	-381.6	-397.2	-383.4	-396.5	-382.8

Table 2
 ΔE° (kJ/mol) for different compounds presented in Figs. 1 and 2

Reactions → Compounds ↓	Hald + UGly		Hald + PGly		Hald + DGly		Hald + GlyZ	
	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous
1	-105.1	-686.5	-	-	-	-	-	-
2	-463.0	-1052.0	-34.1	-13.0	-	-	-	-
2a	-	-	-	-	-3.1	-612.8	-	-
2b	-	-	-	-	-	-	18.7	25.4
3	-0.2	-107.7	428.7	931.2	-	-	-	-
3a	-	-	-	-	45.5	-526.7	1382.7	1114.1
4	92.5	-15.3	521.5	1023.6	-	-	-	-
4a	-	-	-	-	103.7	-479.7	1440.8	1161.1
5	-315.6	-396.3	113.3	642.6	-	-	-	-
5a	-	-	-	-	-411.3	-879.0	925.9	761.8
6	-	-	-	-	-1840.7	-1908.0	-503.6	-267.2
7	-	-	-	-	-463.5	-1010.0	873.7	630.9
Gox	-356.6	-342.2	-355.7	-341.6	-356.8	-342.3	-356.0	-341.9

Table 3
Dipole moments (μ , in Debye) and heats of formation (ΔH_f° , in kJ/mol) of different compounds presented in Figs. 1 and 2

Compounds ↓	μ		ΔH_f° [AM1]
	Gaseous [RB3LYP/ 6-31G(d)]	Aqueous [PCM/ RB3LYP/ 6-31G(d)]	
1	4.2827	5.0434	440.6
2	4.0962	5.0012	-159.3
2a	5.3935	6.6538	-858.8
2b	11.1904	13.9848	-651.9
3	3.3344	4.274	-770.4
3a	8.2771	10.9683	-903.4
4	3.7531	4.9704	-475.7
4a	9.0545	11.4808	-579.7
5	3.5985	5.0321	-388.8
5a	4.7007	6.8696	-507.4
6	1.9301	2.5537	-408.9
7	9.115	11.6541	-751.9
Gox	0.0018	0.002	-241.6

Table 4
 ΔG° (kJ/mol) and ΔE° (kJ/mol) for the formation of NH_3 from Gly species (Fig. 4)

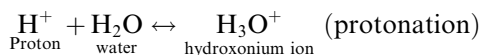
Precursor ↓	ΔG°		ΔE°	
	Gaseous	Aqueous	Gaseous	Aqueous
UGly	-91.8	-116.1	-50.9	-77.1
PGly	121.7	122.7	163.5	442.3
DGly	-900.0	-921.2	-800.7	-823.8
GlyZ	-174.3	-118.5	-132.1	-3.4

[calculated by using $\text{Hald} + \text{NH}_3$ total electronic energies ($E_{\text{Hald}}^\circ + E_{\text{NH}_3}^\circ$) as the standard in the equation $\Delta E^\circ = E_{\text{Product(s)}}^\circ - E_{\text{Reactant(s)}}^\circ$], μ and ΔH_f° for different compounds formed in $\text{Hald} + \text{NH}_3$ reaction are presented in Table 5.

Mass balance of any reaction is important as it is related to the energy changes. The total mass balance of $\text{Hald} + \text{Gly}$ reaction under different pH conditions has been maintained during the calculation of ΔG° and ΔE° . The main problem in balancing the total mass arises for protonation, deprotonation, and addition or elimination of OH^- . Therefore, the following equations have been applied during balancing the total mass (Shipar, 2004a, 2006):

Table 5
 ΔG° (kJ/mol), ΔE° (kJ/mol), μ (Debye) and ΔH_f° (kJ/mol) for different compounds presented in Fig. 5

Reactions → Compounds ↓	ΔG°		ΔE°		μ		ΔH_f°
	Gaseous	Aqueous	Gaseous	Aqueous	Gaseous	Aqueous	
I	-52.1	-342.9	-52.5	-343.3	4.2827	5.0434	440.6
I	-165.8	-452.1	-206.9	-493.1	6.9076	8.0617	225.3
II	27.9	24.2	-13.8	-17.5	2.1878	2.6691	-438.5
III	53.5	52.3	53.9	52.7	1.2492	1.5645	-138.8
IV	-145.1	-419.9	-144.6	-419.4	5.4365	6.4313	504.9
Fald	-1682.3	-1669.2	-1641.0	-1627.9	2.1869	2.6053	-129.5



and deprotonation



(addition and elimination of OH^-)

Moreover, during the production of Gox (Figs. 1 and 2), the eliminated or reproduced UGly and DGly will instantly be protonated to PGly and GlyZ in $\text{Hald} + \text{PGly}$ and $\text{Hald} + \text{GlyZ}$ reactions, respectively. Therefore, the total mass balance will be different due to the difference in reactants and products. This difference in the mass balance has been maintained during the calculation of ΔG° and ΔE° .

According to ΔG° , formation of Gox is assumed plausible in $\text{Hald} + \text{Gly}$ reaction under different pH conditions. The gaseous state reaction is supposed to be more feasible for the production of Gox than that of the aqueous solution (Table 1). It is consistent with the previous finding that the gaseous state $\text{Gald} + \text{Gly}$ (Shipar, 2004b) and $\text{DHA} + \text{Gly}$ (Shipar, in press) reactions are more favorable for the production of methyl glyoxal (MG) than the aqueous solution. However, in both of the gaseous state and aqueous solution, $\text{Hald} + \text{Gly}$ reaction is much more favorable for the production of Gox than the production of MG in $\text{Gald} + \text{Gly}$ (Shipar, 2004b) and $\text{DHA} + \text{Gly}$ (Shipar, in press) reactions. Therefore, the rate of browning in $\text{Hald} + \text{Gly}$ reaction is assumed higher than that of $\text{Gald} + \text{Gly}$ and $\text{DHA} + \text{Gly}$ reactions, and it is consistent with the previous report by Namiki and Hayashi (1983) and Hayashi and Namiki (1986).

$\text{Hald} + \text{DGly}$ reaction is seemed to be the most favorable for the production of Gox in both of the gaseous state and aqueous solution (Table 1). It is in agreement with the previous evaluation that $\text{Gald} + \text{DGly}$ (Shipar, 2004b) and $\text{DHA} + \text{DGly}$ (Shipar, in press) reactions are the most favorable for the production of MG. It is also in agreement with the previous statement that the basic condition facilitates the Maillard reaction (Ames, 1990; Bell, 1997; Davídek et al., 1990; Eskin, 1990; Lea & Hannan, 1949; Macrane et al., 1993). This finding is important as the Maillard reaction can take place in foods as well as in the human body (human blood is slightly basic). However, the gaseous state $\text{Hald} + \text{DGly}$ reaction is not favorable for the production of the Schiff-base, 4a (Table 1). Therefore, the consecutively produced 3a in $\text{Hald} + \text{DGly}$ gas-

eous state reaction (Fig. 2) may eliminate one molecule of H₂O and oxidation may take place at the same time, leading to the production of **5a**, which can sequentially produce Gox. The aqueous state Hald + DGly reaction is feasible for the production of all compounds in the proposed mechanism (Fig. 2 and Table 1), and therefore, it is assumed to be the most feasible for following the general mechanism of the Hodge-scheme (Hodge, 1953) to produce Gox.

According to ΔE° (Table 2), in both of the gaseous state and aqueous solution, **6**, **7** and **5a** are supposed electronically be the most, second most and third most stable species in Hald + DGly reaction, respectively. **2b**, **4a** and **3a** have been found to contain the highest, second highest and third highest dipole moments (μ) in both of the gaseous state and aqueous solution (Table 3). **3a** and **3** have been found to have the lowest and second lowest heats of formation (ΔH_f°) Table 3.

In both of the gaseous state and aqueous solution, Hald + UGly reaction is assumed to be the second most favorable for the production of Gox (Table 1). It is consistent with the previous findings that Gald + UGly (Shipar, 2004b) and DHA + UGly (Shipar, in press) reactions are the second most favorable for the production of MG. However, Hald + UGly gaseous state reaction is found not to be favorable for the formation of addition compound, **3**, and the Schiff-base, **4** (Table 1). Therefore, it is assumed that deprotonation, elimination of H₂O and oxidation may take place at the same time, and **5** is produced from the subsequently formed **2** (Fig. 1), which may lead to the subsequent production of Gox in the gaseous state Hald + UGly reaction. On the other hand, Hald + UGly reaction is not favorable for the formation of **4** in aqueous solution, and therefore, it is assumed that the subsequently formed **3** (Fig. 1) may eliminate one molecule of H₂O and oxidation may take place at the same time, leading to the formation of **5**, which may subsequently produce Gox under this condition.

Based on ΔE° (Table 2), **2**, Gox and **5** are assumed electronically be the most, second most and third most stable species in Hald + UGly gaseous state reaction, respectively. On the other hand, in aqueous solution, **2**, **5** and Gox are seemed electronically be the most, second most and third most stable species in Hald + UGly reaction, respectively (Table 2).

Except the formation of **2** in aqueous solution and Gox in both of the gaseous state and aqueous solution, Hald + PGly reaction is supposed not to be favorable for the formation of all other compounds in the proposed mechanism (Fig. 1 and Table 1). Similarly, except the formation of **2a** in aqueous solution and Gox in both of the gaseous state and aqueous solution, Hald + GlyZ reaction is found not to be favorable for the formation of all other compounds in the proposed mechanism (Fig. 2 and Table 1). Therefore, production of Gox under these conditions is assumed to be hindered. It reveals that nucleophilic addition of Hald with PGly or GlyZ is not feasible because of the unavailability of lone pair electrons on the glycino-

nitrogen. It is consistent with the prior findings that Gald + PGly, Gald + GlyZ (Shipar, 2004b), and DHA + PGly, DHA + GlyZ (Shipar, in press) reactions are less favorable for the formation of MG. It is also 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, it is difficult to explain, and probably, some other composite mechanisms are involved in these cases for the production of Gox. Gox is assumed electronically be more stable in the gaseous state than that of the aqueous solution under all pH condition (Table 2). In both of the gaseous state and aqueous solution, dipole moments (μ) of Gox have been found as the lowest (Table 3).

$\Delta G_{\text{gas}}^\circ$ and $\Delta G_{\text{aq}}^\circ$ for the production of Gox through the oxidation of Hald (Fig. 3) have been calculated as -390.6 and -379.8 kJ/mol, respectively, which reveals that oxidation of Hald to Gox is more favorable in the gaseous state than that of the aqueous solution. It is significant as Gox, produced through the oxidation of Hald, can enhance the rate of browning, and this may be responsible for higher browning activity of Hald than other carbonyl compounds as reported previously (Hayashi & Namiki, 1986; Namiki & Hayashi, 1983). Oxidation of Hald to Gox may take place in Hald + PGly and Hald + GlyZ reactions, and play an important role in producing melanoidines under these conditions.

Due to the link to various pathologies, recent interest of researchers on α -dicarbonyl compounds, e.g. Gox, has significantly been increased (Davidek et al., 1990; Eskin, 1990; Ledl & Schleicher, 1990; Macrane et al., 1993; Meade, Miller, & Gerrard, 2003). Gox is a mutagenic compound, 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 found to be implicated in many degenerative diseases as well as the aging process through the reaction with the amino residues of proteins, resulting in the formation of the advanced glycation end products (AGEs) (Akhand et al., 2001; Leng, Graves, & Chaires, 1998; Odani, Shinzato, Matsumoto, Usami, & Maeda, 1999; Odani et al., 1998; Sady et al., 2000; Reber et al., 2002; 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, less reactivity of Gox than the substituted methyl glyoxal has been observed in the 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 at different computational methods (Bulat & Torolabbé, 2002; Sancho-García, Pérez-Jiménez, Pérez-Jordá, & Moscardó, 2001; Tantirungrotechai, 2003; Zelek, Wasilewski, & Heldt, 2000).

In both of the gaseous state and aqueous solution, oxidation plays an important role during the production of

Gox (Figs. 1–3). Hence, presence of air or oxygen is necessary for the production of Gox from Hald. According to the total mass balance, one molecule of O_2 is required for the production of Gox under all pH conditions (Figs. 1 and 2). During the oxidation of Hald to Gox (Fig. 3), one molecule of O_2 has also been found to be required.

Water is compulsory for the initiation of the Maillard reaction (Ames, 1990; Davídek et al., 1990; Eskin, 1990; Labuza & Saltmarch, 1981; Lea & Hannan, 1949; Macrane et al., 1993; Nursten, 1986). Based on the total mass balance, two molecules of H_2O are required in the initiation step of Hald + UGly, Hald + PGly and Hald + DGly reactions (Figs. 1 and 2), whereas four molecules are required in Hald + GlyZ reaction (Fig. 2). Water is also a by-product in the Maillard reaction (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). During the formation of Gox, two molecules of H_2O have been found to be produced as the by-product in the reaction under all pH conditions (Figs. 1 and 2). Two molecules of H_2O have also been found as the by-product during the oxidation of Hald to Gox (Fig. 3).

According to ΔG° , DGly, GlyZ and UGly are the most, second most and third most favorable for the production of NH_3 , respectively, and PGly is unfeasible for the production of NH_3 , which is also consistent with ΔE° , except for GlyZ in aqueous solution (Table 4). In case of UGly and DGly, the aqueous solution is more feasible for liberating NH_3 , whereas the gaseous phase is more favorable in case of GlyZ. According to the total mass balance, two molecules of H_2O are required for the formation of NH_3 from UGly, whereas one molecule is required for DGly and GlyZ.

NH_3 , liberated from Gly species (Fig. 4), can perform further browning reaction with Hald, leading to the formation of Fald and MeAm (Fig. 5). However, based on ΔG° , formation of **I** and **II** in Hald + NH_3 reaction is found not to be feasible in both of the gaseous state and aqueous solution (Table 5). Therefore, it is assumed that addition of NH_3 to **1** and elimination of one molecule of H_2O may take place at the same time, resulting into the production of **III**, except the production of **I** and **II**, and **III** can consequently lead to the formation of Fald (Fig. 5). The gaseous phase Hald + NH_3 reaction is supposed to be more favorable for the production of Fald than that of the aqueous solution (Table 5). Fald, produced through the reaction between Hald and NH_3 , can become part of melanoidins, and therefore, can affect the rate of browning significantly (Davídek et al., 1990; Eskin, 1990; Macrane et al., 1993). Very little information on the role of Fald (and MeAm), produced during the production of Fald in Hald + NH_3 reaction (Fig. 5) in nonenzymatic browning are known, and therefore, further investigations are necessary. According to ΔE° , Fald is electronically more stable in the gaseous state than that of the aqueous solution (Table 5). On the other hand, **I** contains the highest and **III** contains the lowest μ in both of the gaseous state and aqueous solution, whereas **IV**

contains the highest and **II** contains the lowest ΔH_f° (Table 5). Based on the total mass balance, two molecules of H_2O are found to be required in the initiation step of Hald + NH_3 reaction, and one molecule H_2O is produced as by-product during the production of Fald (Figs. 5).

4. Conclusions

By considering the formation of Gox as one of the possible products, mechanisms for the early stage of Hald + Gly reaction under different pH conditions have been proposed (Figs. 1 and 2). By following the total mass balance of different steps of the reaction, density functional computations at the standard state on the proposed mechanisms have been performed to evaluate the possibility of the formation of different compounds in the proposed mechanisms by estimating ΔG° . Electronic energy changes during the reaction and has been observed through estimating ΔE° . Oxidation of Hald to Gox (Fig. 3) has also been examined by estimating ΔG° . Mechanisms for the liberation of NH_3 from Gly species (Fig. 4), and further browning reaction of NH_3 with Hald (Fig. 5), have also been proposed and tested accordingly at the standard state. The result reveals that formation of Gox is plausible under all pH conditions, and therefore, it is supposed to be one of the most possible intermediates in the reaction. Hald + DGly and Hald + UGly reactions (Figs. 1 and 2) have been found as the most and second most favorable for the production of Gox. The gaseous state reaction is supposed to be more feasible than that of the aqueous solution for the formation of Gox. Hald + PGly and Hald + GlyZ reactions (Figs. 1 and 2) have been found not to be feasible for the formation of almost all intermediates in the reaction, and therefore, production of Gox is assumed to be stalled under these conditions. Some other mechanisms may be implicated for the formation of Gox under these conditions. Oxidation of Hald to Gox (Fig. 3) may take place under these conditions. Production of Gox through the oxidation of Hald (Fig. 3) is assumed more feasible in the gaseous state than that of the aqueous solution. DGly, GlyZ and UGly have been found to be favorable for the production of NH_3 , whereas PGly has been found to be unfavorable. Hald + NH_3 reaction has been found to be more feasible for the formation of Fald in the gaseous state. Gox and Fald (and MeAm), produced through Hald + Gly and Hald + NH_3 reactions, respectively, can perform further reactions to produce various melanoidins. Furthermore, the reactions may follow some other mechanisms to produce various intermediates and melanoidines at different temperatures. Therefore, further investigations are necessary. The theoretical results, presented in this paper, are thought to be helpful for further investigations. Though it is difficult, computational model chemistry could facilitate to study the reaction at different temperatures, which could provide important clues that will be helpful for establishing proper mechanism, leading to find out

appropriate controlling ways of the Maillard reaction in vivo as well as vitro.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.foodchem.2006.07.061.

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