Efficiency of Trapping Methylglyoxal by Phenols and Phenolic Acids

Chih-Yu Lo, Wen-Tuan Hsiao, and Xiu-Yu Chen

Abstract: The carbonyl stress that leads to the formation of advanced glycation end products (AGEs) has drawn much attention recently because of its micro- and macrovascular implications. During monitoring of methylglyoxal (MG), the efficiency of phenolics to directly trap MG can be demonstrated. Twenty compounds consisting of a single benzene ring structure with the addition of at least one hydroxyl group were allowed to react with MG at 37 °C for 1 h under physiological conditions in pH 7.4 phosphate buffer solution. Compounds composed of a benzene structure with a mono-hydroxyl substitute cannot react with MG. Among benzenediols and di-hydroxyl benzoic acids, only hydroquinone reacted with MG and showed a 13% decrease in MG. Nevertheless, high reactivity was shown for 3 benzenetriols. The percentages of MG remaining were 45%, 51%, and 36% for pyrogallol, 1,2,4-trihydroxybenzene, and 1,3,5-trihydroxybenzene, respectively. When a carboxyl group is added to the benzenetriols, steric hindrance and carbon electron charges on the benzene ring are the influential factors in reactivity. Using computational chemistry calculations, a carbon electron charge of −0.24 was the minimum value for high reactivity.

Keywords: carbon electron charge, methylglyoxal, phenolics, phosphate buffer solution, steric hindrance

Introduction

The relationships between many pathological conditions, such as diabetes, aging, and atherosclerosis and carbonyl stress, have drawn much attention in recent decades (Baynes and Thorpe 2000; Ulrich and Cerami 2001; Wondrak and others 2006). Researchers have observed that endogenous reactive carbonyl species (RCS), such as 3-deoxyglucosone (3-DG), glyoxal (GO), and methylglyoxal (MG) (Figure 1), play an important role in mediating carbonyl stress in human cells and are also associated with proliferating signaling pathways and metastasis of several malignancies (Kunitiyasu and others 2002; Sander and others 2003; Abe and others 2004). More RCS are produced where there is a higher concentration of glucose in the physiological system. RCS in the cells can react with proteins, especially lysine and arginine residues, and also with DNA, to form a group of compounds called “advanced glycation end products” (AGEs). These AGEs are irreversible adducts of glucose with proteins and DNA cause structural damage of cells and eventually lead to tissue deterioration or organ failure. It has been shown that an accumulation of AGEs over time in diabetes mellitus can cause micro- or macrovascular complications, such as retinopathy, peripheral neuropathy, and arteriosclerosis (Yamagishi and others 2005; Thornalley 2005). Chemical modifications of the proteins and DNA cause structural damage of cells and eventually lead to tissue deterioration or organ failure. It has been shown that an accumulation of AGEs over time in diabetes mellitus can cause micro- or macrovascular complications, such as retinopathy, peripheral neuropathy, and arteriosclerosis (Yamagishi and others 2005; Thornalley 2005). Therefore, the prevention of the formation and accumulation of RCS and AGEs is now the focus of much research.

Polyphenols commonly exist in plants and in many of our plant foods, including catechins in tea, such as (-)-epicatechin (EC), (-)-epigallocatechin-3-gallate (EGCG); malvidin-3-glucoside in red wine; procyanidins and anthocyanidins in grapes and chocolate; quercetin in onion and apples; and daidzein in soy milk (D’Archivio and others 2007; Yang and others 2008). Polyphenolic compounds are categorized into 4 groups: flavonoids, stilbenes, lignans, and phenolic acids. Many researchers have indicated that polyphenols possess various health beneficial properties, such as antioxidation, antiinflammation, inhibition of carcinogenesis, and antiaging (Vinson and others 2001; Labinskyy and others 2006; Tiapo and others 2007; Koleckar and others 2008). Their scavenging ability for reactive oxygen species and reactive nitrogen species is the major reason for antioxidation (D’Alessandro and others 2003). Several phenolic compounds have been shown to suppress nuclear factor-κB activation that controls a variety of gene expression related to inflammation and carcinogenesis (Fresco and others 1997). Polyphenols, such as resveratrol and EGCG, have also been shown to induce apoptosis of cancer cells (Fresco and others 2006). Therefore, many polyphenols have been research targets because of their potent cancer therapeutic properties.

AGE inhibition has been demonstrated in various synthetic compounds (Rahbar and others 2000). Wu and Yen reported that some flavonoids have better inhibitory effect on AGE formation than aminoguanidine, a well-known AGE inhibitor (Wu and Yen 2005). Our previous study also demonstrated that catechins in green tea and theaflavins in black tea were able to reduce the concentration of MG in simulated physiological conditions (Lo and others 2006). EGCG has been shown to protect against AGE-induced neuronal cell injury and also hindered AGE–AGE receptor interaction-mediated pathway (Lee and Lee 2007). More recently, research showed that polyphenols in green and black tea could trap the RCS produced from lipid oxidation (Zhu and others 2008). In this study, various simple polyphenols were used to investigate the reacting structure pattern existing in the polyphenols.
This study helps us to further understand the reactivity between flavonoids and RCS and the structure pattern that would serve as a foundation for searching better polyphenol candidates for RCS scavenger development.

Materials and Methods

Materials and reagents

Twenty-one different phenolic compounds were tested in this experiment. Phenol, catechol (99%), 3,4-dihydroxybenzoic acid, gallic acid, pyrogallol, EC, MG 40 wt% in water, phosphate buffer solution (PBS) (pH 7.4), and o-phenylenediamine (o-PDA) were purchased from Sigma (St. Louis, Mo., U.S.A.). 3-Hydroxybenzoic acid (99%), 4-hydroxybenzoic acid (99%), 5-hydroxyisophthalic acid (97%), 2,3-dihydrobenzoic acid (99%), 2,4-dihydrobenzoic acid (97%), 2,6-dihydrobenzoic acid (98%), 3,5-dihydroxybenzoic acid (97%), 1,2,4-trihydroxybenzene (99%), 1,3,5-trihydroxybenzene (97%), 2,3,4-trihydroxybenzoic acid (97%), 2-methylquinoline (2-MQ; 97%), and 5-MQ (98%, internal standard) were purchased from Aldrich (St. Louis). Aminoguanidine hydrochloride (98%), resorcinol (98%), and hydroquinone (99%) were purchased from Sigma-Aldrich (St. Louis). Methyl gallate (98%; product of India) and 2,4,6-trihydroxybenzoic acid (≥ 90%; product of U.S.A.) were purchased from Fluka (St. Louis). Aminoguanidine hydrochloride was symbolized as V, mono- or polyphenols were symbolized as shown in Figure 2. Glass threaded vials (14.8 mL; 21 × 70 mm; od × H), high-performance liquid chromatography (HPLC) grade water, and acetonitrile were purchased from Fisher Scientific (Springfield, N.J., U.S.A.).

MG reaction system

Based on 40 wt% MG concentration, 2 mM MG in PBS was prepared. Samples A through V were dissolved in PBS, respectively, with a concentration of 4 mM. All reactants were prepared immediately before the experiment. The reaction model system was as follows: solvent B was increased from 8% to 40% over 10 min, to 80.95% with a flow rate set at 0.8 mL/min. In brief, aliquots of 15 μL were subjected to HPLC analysis. A linear gradient program was performed as follows: solvent B was increased from 8% to 40% over 10 min, to 48% over an additional 2 min, to 60% over an additional 1 min and then back to the starting ratio over an additional 5 min. The 2- and 5-MQ was monitored at 313 nm.

Monitoring the reactivity of compound R in MG PBS

Among the simple polyphenols A to T, R showed the highest reactivity toward MG. Thus, further investigation of R’s reactivity in MG solution was conducted. The reaction was the same as the description in MG Reaction System. After a 37 °C, 1-h reaction, the solution was diluted 100-fold with deionized water and the diluted sample was then ready for mass spectrometric analysis.

Determination of the formation of MG adducts of compound R using liquid chromatography electrospray ionization mass spectrometry (LC-ESI-MS)

The mass spectrum was acquired using a ThermoFinnigan model LQX (San Jose, Calif., U.S.A.) ion-trap mass spectrometer equipped with an ESI source interference and controlled by Xcalibur 2.06. The instrument was coupled with a Surveyor HPLC binary pump. High purity nitrogen was used as nebulizing gas. The mass spectra were acquired in a negative ion mode, a sheath gas flow rate of 75 μL/min, a capillary temperature of 275 °C, a capillary voltage of −19 V, and a tube lens of −80.95 V, with a full ion scan in the range 150 to 330 amu. The direct infusion of the sample was set at 10 μL/min.

Chemistry assistant software

The relationships between reaction activity and physical and chemical properties of phenolic compounds are discussed further. CS Chem 3D Pro 12.0 (Copyright © 1986 to 2009 by CambridgeSoft Corp. [Cambridge, Mass., U.S.A.]) was the software used in the calculation of electron charges for compound A to U.

Results and Discussion

Reaction of MG and polyphenols

It has been shown that MG reacted with major components of green and black teas, such as catechins and theaflavins (Lo and
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In the same molar concentration of catechins and theaflavin, almost twice the amount of MG could be trapped by theaflavins as compared to the catechins, which implies that there were 2 active sites in theaflavins but only one active site in catechins for MG trapping. Theaflavins, the dimers of catechins, can be generated in black tea through the fermentation process or chemically synthesized by peroxidase (Sang and others 2004). As shown in chemometric outcomes, the RCS trapping site in catechin was not blocked in its dimer structure in theaflavins. Before random screening of large numbers of flavonoids, a systematic study was necessary to speed up the selection process of potential RCS trapping agents. According to the number of hydroxyl (−OH) groups on the benzene ring, A to U were the compounds systematically chosen. Compounds A to E consisted of 1 −OH group, F to M contained 2 −OH groups, and 3 −OH groups were found in N to T. U was EC, a flavanol, and it comprised a C₆-C₃-C₆ configuration and 5 −OH groups in the structure. V was the guanidine structure that is a...

Figure 2–The phenolic standards in this experiment.
common drug used in diabetic treatment. Figure 3 represented the chromatographic analysis for compound R and MG after 1 h reaction and e-PDA derivatization. The retention time for 2- and 5-MQ was at 12.85 and 15.35 min, respectively. Compounds A to V had been checked by HPLC and their retention times did not interfere with the detection of 2MQ.

In the investigation, the molar ratio of investigated compound to MG was 1. Special attention was focused on the potent diabetic drug V (guanidine), as it was the positive control in the MG-trapping efficiency study. As shown in Table 1, only 20.61% of MG remained after 1-h incubation of MG with guanidine. Approximately 4/5 of MG was trapped by guanidine.

The scavenging efficiency among A to E (only 1 –OH substituent on benzene ring) was very low. A is the simplest phenolic structure in this study. B to E contain at least 1 –COOH group on the benzene ring and the –OH group locates at positions 2 to 5. From the remaining MG as shown in Table 1, MG was very stable after 1-h incubation with B to E. B to E, compounds with 1 –OH and 1 or 2 –COOH, did not have the ability to trap MG. F to M are compounds with 2 –OH groups on the benzene ring. The 2 –OH groups of F to H are at positions C1 and C2, C1 and C3, and C1 and C4, respectively. I to M are compounds with 2 –OH on various carbon positions, with an additional –COOH group. In this subgroup, with the exception of G and H compounds, the MG remaining levels were the same as the control groups. However, only 5.47% and 12.70% MG reacted with G and H, respectively. From the above results, we can conclude that among benzenediols, the order of reactivity of dihydroxybenzene with MG in simulated physiological conditions was para-(H) > meta- (G) > ortho-benzenediol (F). On the other hand, when comparing H and J, even though compound J had a para-diol structure, an additional –COOH group dramatically reduced its MG trapping ability. This caused the remaining MG level to increase from 87.30% (in H) to 99.83% (in J).

Compounds N to T are benzenetriols. N to P are 3 simple benzenetriol isomers, 1,2,3– (N), 1,2,4– (O), and 1,3,5– (P) benzenetriol. Q to S have 1 –COOH group in addition to

Figure 3—Representative chromatogram of 2- and 5-MQ in the reaction of MG and phenols. Peak 1 is 2-MQ and Peak 2 is 5-MQ.

Table 1—MG remaining percentage after 1-h incubation (%) in pH 7.4 PBS from comparison to 0 h samples (MG-0) and electron charges on carbon number1 to 6 for compound A to T.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>MG (%)</th>
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<tr>
<td>MG-0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MG-1</td>
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<td></td>
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<td></td>
<td></td>
<td>99.19 ± 0.97</td>
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<tr>
<td>A</td>
<td>0.25</td>
<td>−0.10</td>
<td>−0.02</td>
<td>−0.08</td>
<td>−0.02</td>
<td>−0.10</td>
<td>101.94 ± 0.91</td>
</tr>
<tr>
<td>B</td>
<td>−0.07</td>
<td>0.28</td>
<td>−0.10</td>
<td>0.01</td>
<td>−0.08</td>
<td>0.01</td>
<td>100.54 ± 0.30</td>
</tr>
<tr>
<td>C</td>
<td>0.01</td>
<td>−0.08</td>
<td>0.25</td>
<td>−0.08</td>
<td>−0.02</td>
<td>−0.05</td>
<td>100.38 ± 0.44</td>
</tr>
<tr>
<td>D</td>
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<td>0.01</td>
<td>−0.10</td>
<td>0.28</td>
<td>−0.10</td>
<td>0.01</td>
<td>98.83 ± 0.72</td>
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<td>E</td>
<td>0.01</td>
<td>−0.02</td>
<td>0.01</td>
<td>−0.06</td>
<td>0.24</td>
<td>−0.06</td>
<td>100.15 ± 0.06</td>
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<tr>
<td>F</td>
<td>0.19</td>
<td>0.19</td>
<td>−0.11</td>
<td>−0.08</td>
<td>−0.08</td>
<td>−0.11</td>
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<td>G</td>
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<td>−0.19</td>
<td>0.26</td>
<td>−0.16</td>
<td>−0.01</td>
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<td>94.53 ± 0.32</td>
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<td>H</td>
<td>0.21</td>
<td>−0.19</td>
<td>−0.10</td>
<td>0.21</td>
<td>−0.09</td>
<td>−0.10</td>
<td>87.30 ± 0.11</td>
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<td>98.83 ± 0.31</td>
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<td>K</td>
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<td>−0.16</td>
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<td>−0.09</td>
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<td>−0.10</td>
<td>−0.04</td>
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<td>M</td>
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<td>0.25</td>
<td>−0.16</td>
<td>0.25</td>
<td>−0.13</td>
<td>100.99 ± 0.11</td>
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<td>N</td>
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<td>0.12</td>
<td>0.19</td>
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<td>−0.08</td>
<td>−0.18</td>
<td>45.16 ± 0.06</td>
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<td>−0.19</td>
<td>0.21</td>
<td>−0.15</td>
<td>−0.10</td>
<td>90.76 ± 0.19</td>
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<td>P</td>
<td>0.26</td>
<td>−0.24</td>
<td>0.26</td>
<td>−0.24</td>
<td>0.26</td>
<td>−0.24</td>
<td>35.76 ± 0.55</td>
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<td>Q</td>
<td>−0.11</td>
<td>0.21</td>
<td>0.11</td>
<td>0.21</td>
<td>−0.14</td>
<td>−0.04</td>
<td>96.59 ± 0.12</td>
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<td>0.29</td>
<td>−0.24</td>
<td>0.28</td>
<td>−0.24</td>
<td>0.29</td>
<td>25.43 ± 0.11</td>
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<td>S</td>
<td>−0.04</td>
<td>−0.13</td>
<td>0.18</td>
<td>0.15</td>
<td>0.19</td>
<td>−0.13</td>
<td>88.89 ± 1.64</td>
</tr>
<tr>
<td>T</td>
<td>−0.05</td>
<td>−0.33</td>
<td>0.18</td>
<td>0.15</td>
<td>0.18</td>
<td>−0.14</td>
<td>94.93 ± 0.14</td>
</tr>
<tr>
<td>U</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>V</td>
<td></td>
<td></td>
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<td></td>
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<td>20.61 ± 0.07</td>
</tr>
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*Values are mean ± 1/2 range.

© Carbon numbers are coordinated with structures in Figure 2.
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3 –OH groups. T, methyl gallate is a methyl ester of S, gallic acid. The remaining MG of this subgroup seen in Table 1 shows the highest level was in Q (96.59%), followed by T (94.93%), S (88.89%), and O (50.76%). Compounds: N (45.16%), P (35.76%), R (25.43%) had less than 50% MG remaining. This indicates the influence of –OH numbers and positions on reactivity. Three –OH groups are necessary for the benzene type of compounds to have significant reactivity in MG trapping reaction. However, the forth substitute, such as –COOH or its methyl ester, could not be next to 3 successive –OH, for example, in Q, or be directly opposite to 3 successive –OH, such as in S and T. The best configuration for MG trapping reaction was 2,4,6-trihydroxybenzoic acid (R: 74.57%) and R without carboxylic group (1,3,5-trihydroxybenzene [P: 64.24%]). The summary from these 3 subgroups with 1, 2, or 3 –OH groups can be concluded as: the benzene compounds with 1 and 2 –OH were not efficient for MG trapping reaction. At least half of the benzenetriol isomers had higher reactivity with MG. However, an appropriate position for a carboxylic group played a key role in the reaction.

Computational chemistry elucidation

With the assistance of computer software used for physical and chemical property calculations, the carbon charges on a benzene ring were further calculated. Using CS Chem 3D Pro 12.0, charges were calculated and are listed in Table 1. The charges of all 6 carbons on a benzene ring were −0.03 (not listed). The following comparisons were based on this number.

Compound A with the addition of a single –OH substitute no longer had carbon charges exactly equal to −0.03. That is because the electron-attracting ability of a substituent, such as an –OH, was larger than the carbon atom. This gave the carbon that attached to the oxygen (C∗−OH) a positive charge. However, the electron attracting power among para, meta, or ortho carbons was not equal. For the ring carbons having negative electron charges in compound A, the carbons in ortho position (−0.10) had the largest absolute value, followed by para (−0.08) and then meta position (−0.02).

Compounds B, C, and D were isomers with one carboxyl substituent to compound A. Their carbon charges were calculated by CS Chem 3D Pro 12.0. The distribution of electrons in benzene ring of these compounds was more complicated than A. The only phenomenon that could be concluded from these 3 compounds was that the carbons that covalently bound to the hydroxyl group (C∗−OH) had positive charges. The carbons with a carboxyl group attached (C∗−COOH) did not necessarily show a positive or negative charge. C∗−COOH position relative to C∗−OH was the major factor for charge determination. The high electronnegative oxygen atom in a hydroxyl group has a large electron-attracting inductive effect regardless of the position of carboxyl groups. This was found in all C∗−OH that showed positive charges for all the compounds in this study (A to U). The values of C∗−OH were between 0.24 and 0.28 in A to E. Other carbons, without a substituent, showed absolute values between 0.01 and 0.10, and these electron charge values gave no trapping ability for MG (Table 1).

The same tendency for C∗−OH and C∗−COOH occurred in compounds F to M. C∗−OH in benzenetriol isomers F to H were positive and the rest of the carbon charges were negative. In benzoic acid with 2 –OH groups, C∗−OH still remained positive; however, the C∗−COOH in M, which was in meta position to both hydroxyl groups, was positive. The unsubstituted carbon charges were between 0.01 and 0.19 in absolute value in F to H and between 0.06 and 0.16 in absolute value of I to M, excluding a positive value in K. From these calculated values, there was relative small (12.70% in H) or no MG trapping activity in F to M. No reasonable explanation can be found for compound H at this time.

No exceptional negative charges were found in C∗−OH in N to T. When hydroxyl groups increased to 3 on the benzene ring, no matter with or without a carboxyl substituent, non-OH attached carbons became negatively charged. The −0.08 was the largest charge value for unsubstituted carbon in benzenetriol isomers (N to P). The smallest carbon charge among N to P was −0.24. The low charge (−0.24) of the 3 unsubstituted carbons in P was contributed to by its symmetry property. This led to a 64% MG decrease after 1-h incubation. Q to S were the isomers with 3 OH and 1 COOH. The huge differences in MG trapping efficiency (3%, 75%, and 11% for Q, R, and S, respectively) can be elucidated from a carbon charge analysis. The carbon charges, for C-5 and C-6 in Q were −0.14 and −0.04, respectively, and for symmetrical C-2 and C-6 in S were −0.13. Therefore, the trapping efficiency was low in both compounds. R, which was P with one carboxyl substituent on the benzene ring, showed that carboxyl substituent tended to induce a stronger MG trapping activity even though the same negative charges were shown on P and R for unsubstituted carbons (−0.24). Nevertheless, an extraordinarily low carbon charge (−0.33) was found on C-2 of T but no high MG trapping outcome was found. Only 5% MG reaction with T was observed after 1-h incubation. This may imply that a steric hindrance was an overwhelming factor in MG nucleophile substitution.

The above observations were on reactions between simple benzene ring structures with various numbers of hydroxyl groups or a single carboxylic acid substituent and MG. A more complicated compound, EC, one of the flavan-3-ol in green tea polyphenols, was chosen for further illustration. The carbon electron charges on EC (structure U) were calculated and are shown in Figure 4. Eight of 15 carbons had negative charges with the carbon on position 6 showing the lowest number, −0.26, and the carbon on position 8 showing the 2nd lowest number, −0.25. The MG scavenging percentage was high in U (91.35%). Therefore, EC is representative of the high correlation between MG reactivity and low negative carbon electron charges. This result corresponds with the previous study that showed positions 6 and 8 were the MG reaction sites for epigallocatechin gallate (Lo and others 2006; Todani and Peterson 2006; Sang and others 2007). Looking at polyphenols A

Figure 4–The carbon electron charges on EC.
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Figure 5—The mass spectrum of the reaction products in the system of 2,4,6-trihydroxy-benzoic acid (compound R) and methylglyoxal.

Polyphenolic composition
In order to further understand the products of polyphenol and MG reaction, the reaction product of R, 2,4,6-trihydroxybenzoic acid, and MG was subjected to LC-ESI-MS direct infusion analyses. The result is shown in Figure 5. The spectrum was consistent with the possible MG adducts. As seen in Figure 5, MS analysis showed a pseudomolecular ion at 169 [M-H]$^-$ for compound 1 and it was R. This indicated the presence of unreacted polyphenol in the system. Similarly, base peak in this spectrum for compound 2 showed a pseudomolecular ion at 241 [M+72-H]$^-$ that corresponds to R with mono-MG adduct. The ion at m/z 223 suggested a loss of water in compound 2. Furthermore, compound 3 represented a pseudomolecular ion at 313 [M+144-H]$^-$ that structure corresponds to R with di-MG adduct. Consequently, compound 2 was able to react with MG to produce a di-MG adduct.

Conclusions
In conclusion, these results showed high reactivity of MG and certain polyphenols with specific chemical structural arrangements. Computational chemistry analysis can provide a potentially important screening tool for compounds with favorable effects for the control of carbonyl stress.

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