



# Interaction of free arginine and guanidine with glucose under thermal processing conditions and formation of Amadori-derived imidazolones



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## ABSTRACT

To investigate the reactivity of free guanidine and arginine in the formation of imidazolinone derivatives, model systems of guanidine or arginine/glucose or  $^{13}\text{C}$ -6-glucose were heated in aqueous solutions at 110 °C for 3 h and the residues were analyzed by ESI/qTOF/MS using MS/MS and isotope labeling techniques. The analysis of the data indicated that guanidine and arginine formed both covalent and non-covalent interaction products. Covalent interactions included Amadori rearrangement at the  $\alpha$ -nitrogen with glucose and imidazolinone formation with 3-deoxy-glucosone at the guanidine side-chain. Non-covalent interactions, such as self-interaction and interaction with free guanidine or arginine and glucose, were also observed. Guanidine underwent three sequential Amadori rearrangements and the free and mono-glycated guanidine also formed imidazolinone derivatives and their corresponding dehydration products and at the same time exhibiting various non-covalent interactions. On the other hand, arginine formed free Amadori product, free imidazolinone and Amadori-derived imidazolinone derivative in addition to methylglyoxal-derived hydroimidazolones.

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## 1. Introduction

Glycation refers to the modification of amino groups in proteins and peptides with reducing sugars under physiological conditions as well as under conditions of food processing, storage, and cooking (Hayase, 2000). This modification mostly affects the side-chains of lysine and arginine residues and produces advanced glycation end-products (AGEs). As arginine residues are often localized in active, allosteric, and metal-binding centers of enzymes, their glycation may also alter the physiology of the corresponding organs and tissues (Frolov, Schmidt, Spiller, Greifenhagen, & Hoffmann, 2014). Typical arginine modifications are dihydroxyimidazolines, imidazolinones, and imidazolones (Van Lancker, Adams, & De Kimpe, 2011). Imidazolinone or imidazolone derivatives arise from the interaction of guanidine moiety in arginine with 1,2-dicarbonyl compounds (Hayase, Konishi, & Kato, 1995). Several glyoxal- and methylglyoxal-derived arginine-related adducts, such as glyoxal-derived hydroimidazolone (Glarg), carboxymethylarginine (CMA), methylglyoxal-derived hydroimidazolones (MG-H1, MG-H2 and MG-H3) have been reported in the literature (Schmidt, Böhme, Singer, & Frolov, 2015). Incubation of  $N^{\alpha}$ -tert-butoxycarbonyl (Boc)-arginine with methylglyoxal

yielded 2-amino-5-(2-amino-4-hydro-4-methyl-5-imidazolinone-1-yl)pentanoic acid (MG-H3), which can slowly hydrolyze to  $N^{\delta}$ -(5-methyl-4-oxo-5-hydroimidazolinone-2-yl)-lornithine (MG-H1) (Klöpper, Spanneberg, & Glomb, 2011). Frolov et al. (2014) reported that the precursor compound dihydroxy-imidazolidine yielded glyoxal (Glarg) and methylglyoxal-derived hydroimidazolones (MG-H), with Glarg being further degraded to carboxymethyl-L-arginine (CMA) (Frolov et al., 2014). In addition, 3-deoxyglucosone is also a well-known reactive 1,2-dicarbonyl compound and may form imidazolinone and imidazolone derivatives through reaction with guanidine moiety in proteins and peptides with significant health implications (Godfrey, Yamada-Fowler, Smith, Thornally, & Rabbani, 2014). The 3-deoxyglucosone can be generated from Amadori compounds in the early stage of the Maillard reaction (Niwa, 1999), and undergo further reactions with free amino groups to form imidazolinone and imidazolone. The formation of imidazolone by incubating 3-deoxyglucosone with arginine is very fast, reaching a maximum concentration within 24 h (Niwa et al., 1997). Research found that incubation of 3-deoxyglucosone with  $N^{\alpha}$ -benzoylarginine amide lead to the formation of two diastereomeric dihydroxyimidazolines and imidazolone (Hayase, Konishi, & Kato, 1995; Konishi, Hayase, & Kato, 1994). Additionally, the formation of bicyclic minor compounds derived from one molecule of  $N^{\alpha}$ -benzoylarginine amide and two molecules of 3-deoxyglucosone was also observed by the same

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group (Hayase, Koyama, & Konishi, 1997). Currently, imidazolinones are considered to arise from the reaction of arginine residues in proteins or peptides with 3-deoxy-glucosone after a hydrolytic step (Henle, Walter, Haeßner, & Klostermeyer, 1994). The purpose of this study was to investigate formation of such moieties from free arginine and guanidine under standard thermal processing conditions using qTOF-ESI MS/MS and the isotope-labeling technique.

## 2. Materials and methods

### 2.1. Materials and reagents

High-purity (>98%) L-arginine, L-ornithine hydrochloride, guanidine hydrochloride, D-glucose, and potassium hydroxide (KOH) were purchased from Sigma-Aldrich Chemical Co. (Oakville, ON, Canada). The [6-<sup>13</sup>C]glucose (99%) was purchased from Cambridge Isotope Laboratories (Andover, MI).

### 2.2. Sample preparation

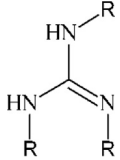
Model systems (10 mg) consisting of guanidine (HCl)/glucose (1:1 M ratio), guanidine (HCl)/glucose (2:5 M ratio) and arginine/

glucose (1:4 M ratio) were dissolved in water (1 mL) and heated on a sand bath in an open vial (5 mL capacity) at 110 °C for 3 h until dry (see Table S1). The arginine/glucose (1:1 M ratio) samples were dissolved in water (2 mL) and heated on a sand bath in an open vial (5 mL capacity) at 110 °C for 3 h (until dry). The reaction mixtures were subsequently analyzed by qTOF/ESI/MS. Arginine (1 mg) was analyzed by pyrolysis gas chromatography-mass spectrometry (Py-GC/MS) for the volatile content. All the samples were analyzed in duplicates.

### 2.3. Quadrupole time of flight/electrospray ionization mass spectrometry (qTOF/ESI/MS) analysis

Samples were analyzed according to previously published procedures (Nashalian & Yaylayan, 2015). In summary the dry reaction mixtures were dissolved in LC-grade water to a concentration of 1 mL/mg. The samples were then diluted 10-fold in 10% methanol prior to analysis by qTOF/ESI/MS. The qTOF/ESI/MS system was comprised of a Bruker Maxis Impact quadrupole-time of flight mass spectrometer (Bruker Daltonics, Bremen, Germany) operated in positive ion mode. Samples (1 µL) were injected directly into the qTOF/ESI/MS. Instrument calibration was performed using sodium

**Table 1**  
Elemental composition and isotope incorporation in Amadori products of guanidine originating from guanidine (HCl)/glucose 1:1 M ratio model system heated at 110 °C for 3 h (see Fig. 1).

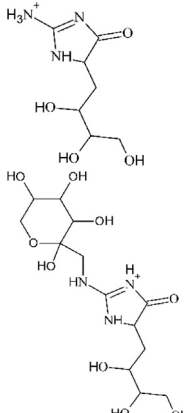
	[M+H] <sup>+</sup>	Elemental composition	Error (ppm)	[6- <sup>13</sup> C]Glucose atoms
2 × R = H	222.1084 (186.0880) <sup>a</sup>	C <sub>7</sub> H <sub>16</sub> N <sub>3</sub> O <sub>5</sub> (C <sub>7</sub> H <sub>12</sub> N <sub>3</sub> O <sub>3</sub> )	2.7 0.7	One
1 × R = H	384.1616 (222.1086) <sup>a</sup>	C <sub>13</sub> H <sub>26</sub> N <sub>3</sub> O <sub>10</sub> (C <sub>7</sub> H <sub>16</sub> N <sub>3</sub> O <sub>5</sub> )	0.6 0.7	Two
0 × R = H	546.2174 <sup>b</sup> (384.1616) <sup>a</sup> (222.1086) <sup>a</sup>	C <sub>19</sub> H <sub>36</sub> N <sub>3</sub> O <sub>15</sub> (C <sub>13</sub> H <sub>26</sub> N <sub>3</sub> O <sub>10</sub> ) (C <sub>7</sub> H <sub>16</sub> N <sub>3</sub> O <sub>5</sub> )	5.1 1.8 1.8	Three

R = Fructosyl moiety or H.

<sup>a</sup> MS/MS fragment.

<sup>b</sup> Also shows an ion at [M–H<sub>2</sub>O+H]<sup>+</sup> = 528.2039 with elemental formula of C<sub>19</sub>H<sub>34</sub>N<sub>3</sub>O<sub>14</sub> (0.33 ppm error).

**Table 2**  
Calculated elemental composition and isotope incorporation in imidazolinone derivatives of guanidine originating from guanidine(HCl)/glucose 1:1 M ratio model system heated at 110 °C for 3 h (see Fig. 2).

Structure	[M+H] <sup>+</sup>	Elemental composition	Error (ppm)	[6- <sup>13</sup> C]Glucose atoms
	204.0978 (186.0872) <sup>a</sup>	C <sub>7</sub> H <sub>14</sub> N <sub>3</sub> O <sub>4</sub> C <sub>7</sub> H <sub>12</sub> N <sub>3</sub> O <sub>3</sub>	1.2 3.6	One
	366.1501 (348.1397) <sup>a</sup>	C <sub>13</sub> H <sub>24</sub> N <sub>3</sub> O <sub>9</sub> C <sub>13</sub> H <sub>22</sub> N <sub>3</sub> O <sub>8</sub>	1.24 2.84	Two

<sup>a</sup> [M–H<sub>2</sub>O+H]<sup>+</sup>.

**Table 3**

Calculated elemental composition and isotope incorporation in the products originating from covalent and non-covalent interactions of arginine/glucose model systems heated at 110 °C for 3 h and shown in Figs. 3 & S1.

[M+H] <sup>+</sup>	Elemental composition	Error (ppm)	[6- <sup>13</sup> C]Glu incorporation
625.2568 <sup>b</sup>	C <sub>42</sub> H <sub>87</sub> ClN <sub>8</sub> O <sub>32</sub> (+2)	2.5	ND
481.2121 <sup>b</sup>	C <sub>18</sub> H <sub>33</sub> N <sub>4</sub> O <sub>11</sub>	5.2	2
251.1108 <sup>a</sup>	C <sub>9</sub> H <sub>16</sub> N <sub>4</sub> NaO <sub>3</sub>	4.8	ND
337.1714 <sup>a</sup>	C <sub>12</sub> H <sub>25</sub> N <sub>4</sub> O <sub>7</sub>	2.7	1
319.1614 <sup>a</sup>	C <sub>12</sub> H <sub>23</sub> N <sub>4</sub> O <sub>6</sub>	1.1	1
251.1108 <sup>a</sup>	C <sub>9</sub> H <sub>16</sub> N <sub>4</sub> NaO <sub>3</sub>	4.8	0
349.2307 <sup>a</sup>	C <sub>12</sub> H <sub>29</sub> N <sub>8</sub> O <sub>4</sub>	1.4	0
MS/MS of 483.2193 <sup>c</sup>	C <sub>16</sub> [ <sup>13</sup> C <sub>2</sub> ]H <sub>33</sub> N <sub>4</sub> O <sub>11</sub>	ND	2
465.2093	C <sub>16</sub> [ <sup>13</sup> C <sub>2</sub> ]H <sub>33</sub> N <sub>4</sub> O <sub>10</sub>	22	2
320.1636	C <sub>11</sub> [ <sup>13</sup> C <sub>1</sub> ]H <sub>23</sub> N <sub>4</sub> O <sub>6</sub>	18.6	1
166.0968	C <sub>5</sub> [ <sup>13</sup> C <sub>1</sub> ]H <sub>13</sub> O <sub>5</sub>	34	1
112.0867	C <sub>5</sub> [ <sup>13</sup> C <sub>1</sub> ]H <sub>7</sub> O <sub>2</sub>	26	1

ND, not determined.

<sup>a</sup> Model system prepared using 1:1 M ratio and heated 3 h in 2 mL water.

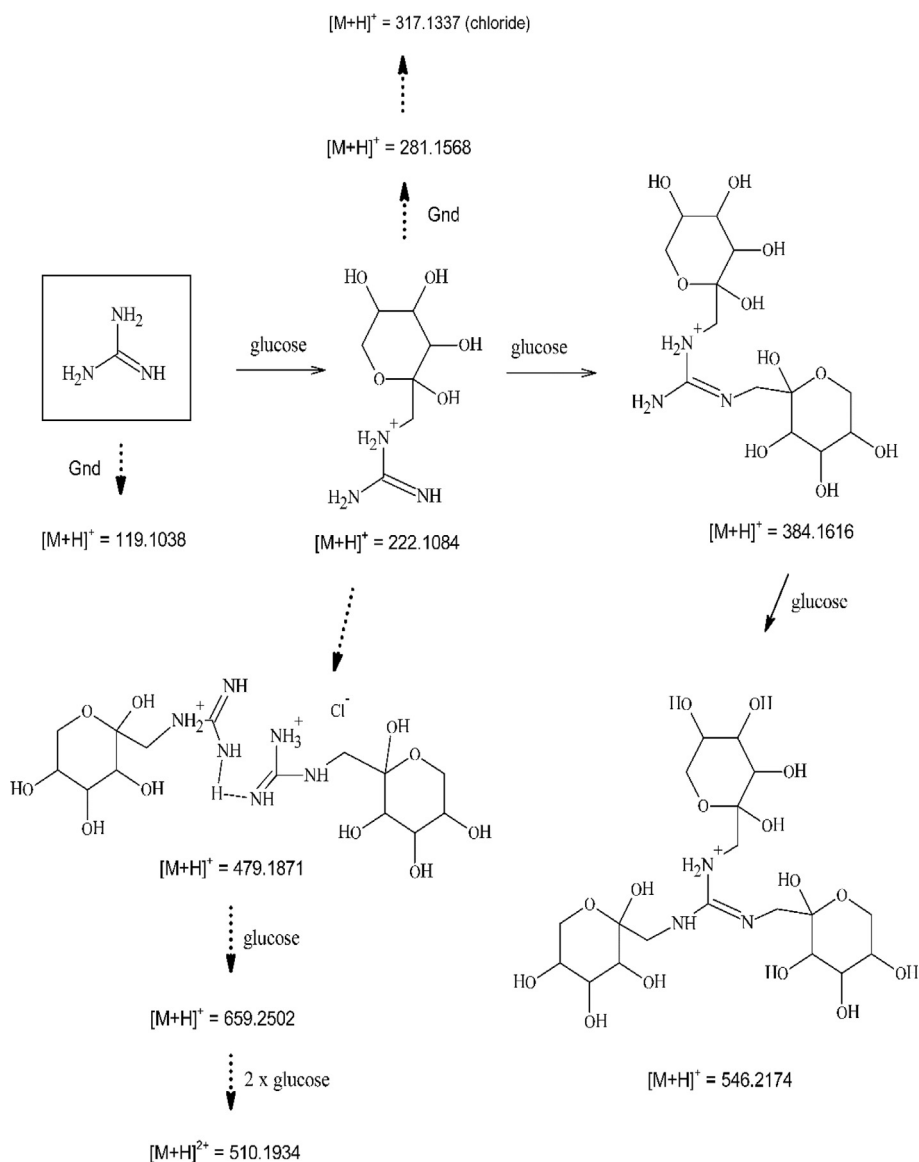
<sup>b</sup> Model system prepared using 1:4 M ratio and heated 3 h in 1 mL water.

<sup>c</sup> Ion corresponding to 481.2121 generated from arginine/[<sup>13</sup>C-6]-glucose model system (see Fig. S1).

formate clusters. The electrospray interface settings were the following: nebulizer pressure 0.6 bar, drying gas 4 L/min, 180 °C, capillary voltage 4500 V. Scan range was from *m/z* 100–1000. The data were analyzed using Bruker Compass Data Analysis software version 4.1. Tandem mass spectrometry (MS/MS) was carried out in MRM mode using collision energies from 15.0–40.0 eV, which were determined by the ions studied.

#### 2.4. Thermal desorption by pyrolysis gas chromatography-mass spectrometry (Py-GC/MS)

Samples were analyzed according to previously published procedures (Nashalian & Yaylayan, 2014). In summary a Varian CP-3800 gas chromatograph coupled to a Saturn 2000 ion trap detector connected to a CDS Pyroprobe 2000 unit through a valved interface (CDS 1500) was used for the desorption of the volatiles from the arginine model. For each analysis, approximately 1 mg of sample was weighed into a quartz tube (0.3 mm thickness), sealed with glass wool and inserted into the pyroprobe and pyrolyzed for 20 s at 250 °C. The separation was performed using a fused silica DB-5MS column (50 m length × 0.2 mm i.d. × 33 μm



**Fig. 1.** Covalent and non-covalent (dotted arrows) interactions of guanidine (Gnd) in the presence of glucose (see Tables 1 and S2).

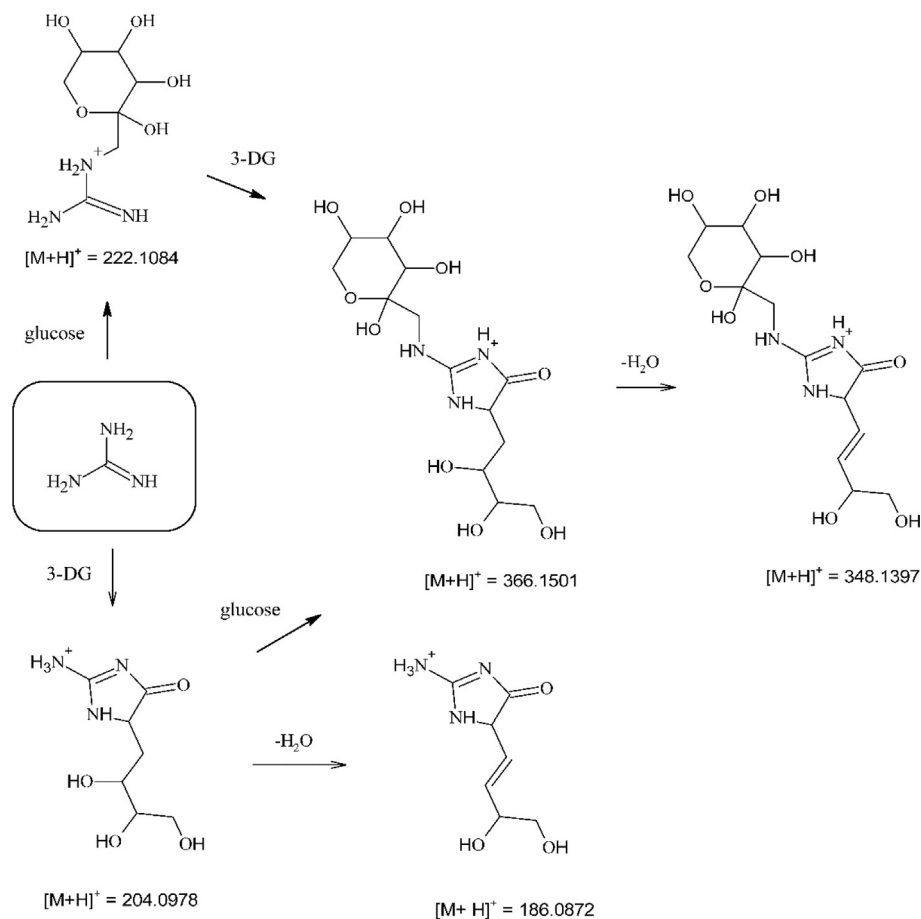


Fig. 2. Covalent interactions of guanidine with 3-deoxyglucosone (3-DG) and glucose (see Table 2).

film thickness; J&W Scientific). The GC method used for the analysis of the volatiles was as follows: GC column flow rate was regulated by an electronic flow controller (EFC) and set at a pressure pulse of 55 psi for first 3 min then decreased to 32 psi at the rate of 300 psi/min and finally increased to 70 psi at a rate of 1.23psi/min for the rest of the run. The GC oven temperature was set at  $-5^{\circ}\text{C}$  for the first 5 min using CO<sub>2</sub> as the cryogenic cooling source and then increased to  $50^{\circ}\text{C}$  at a rate of  $50^{\circ}\text{C}/\text{min}$ . Then, the oven temperature was again increased to  $270^{\circ}\text{C}$  at a rate of  $8^{\circ}\text{C}/\text{min}$  and kept at  $270^{\circ}\text{C}$  for 5 min. The samples were detected by using an ion-trap mass spectrometer. The MS transfer-line temperature was set at  $250^{\circ}\text{C}$ , manifold temperature was set at  $50^{\circ}\text{C}$ , and the ion-trap temperature was set at  $175^{\circ}\text{C}$ . An ionization voltage of 70 eV was used, and EMV was set at 1600 V. The generated data were analyzed using the AMDIS 32 version 2.69 computer software and peak identification was done using the NIST version 2.0 mass spectral research program.

#### 2.4.1. Structural identification

Evidence for the proposed structures of non-volatile reaction intermediates was provided through qTOF/ESI/MS analysis of their elemental composition, MS/MS data and by isotope labeling studies.

### 3. Results and discussion

To understand the chemistry of the guanidine moiety in arginine under high temperature reaction conditions, the guanidine (HCl)/glucose model systems were heated in aqueous solutions at

$110^{\circ}\text{C}$  for 3 h and the dry residues were analyzed by ESI/qTOF/MS, with the major ions observed listed in Tables 1 and 2 and S2. These ions were not generated in the arginine/glucose model systems listed in Table 3, which suggested that the guanidine group of arginine was not released during the Maillard reaction. In theory, the guanidine group of arginine can be released to produce free guanidine and 2-amino-4-pentenoic acid. Even under more drastic pyrolytic conditions ( $250^{\circ}\text{C}$ ) the main degradation product of arginine, identified by Py-GC/MS analysis, was ornithine. It has been shown that ornithine could be formed from arginine by glycation (Sell & Monnier, 2004) and it could be used as a marker of arginine damage (Sell & Monnier, 2005). Interestingly, the analysis of guanidine and arginine model systems indicated the formation of both covalent and non-covalent interaction products.

#### 3.1. Reactions of guanidine in the presence of glucose

Similar to amino acids, guanidine can react with glucose via its amino groups to form Schiff bases or Amadori rearrangement products. Up to three glucose molecules can be condensed with guanidine. The mono-, di- and tri-condensed Amadori rearrangement products were observed in the guanidine (HCl)/glucose model (1:1 M) system at  $[M+H]^+ = 222$ , 384 and 546, respectively (Table 1 and Fig. 1). All the observed ions above had incorporated the expected number of labeled glucose atoms and exhibited the expected elemental formulas (Table 1). To confirm the structure of the Amadori rearrangement products, the MS/MS spectra of the ions at  $[M+H]^+ = 222$ , 384 and 546 generated in the guanidine

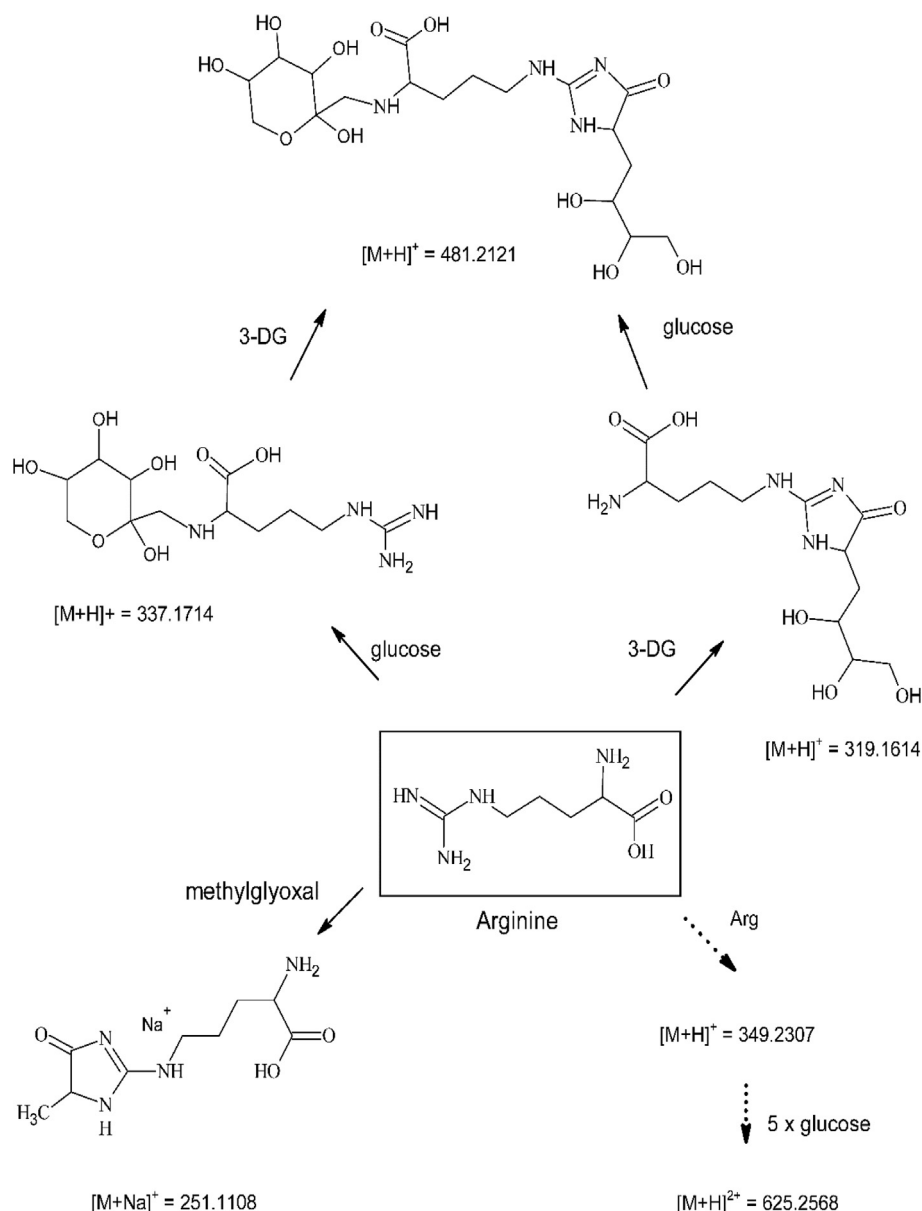


Fig. 3. Covalent and non-covalent (dotted arrows) interactions of arginine (Arg) with glucose and 3-deoxyglucosone (3-DG) (see Table 3).

(HCl)/glucose model systems were recorded (Table 1). The observed MS/MS fragmentation pattern represented the loss of water or glucose moieties from the Amadori rearrangement products, supporting the proposed structures. Furthermore, under the reaction conditions the free guanidine was able to react with 3-deoxyglucosone (Saraiva, Borges, & Florêncio, 2006) to form the imidazolinone at  $[M+H]^+ = 204$  (see Fig. 2 and Table 2) and its dehydration product at  $[M+H]^+ = 186$ . Both of the above ions also underwent Amadori rearrangement with glucose to produce the sugar adducts at  $[M+H]^+ = 366$  and  $348$  (Fig. 2). Alternatively, these ions could also arise from the interaction of guanidine Amadori product observed at  $[M+H]^+ = 222$  with 3-deoxyglucosone, followed by dehydration. The above observations may indicate the ability of guanidine Amadori product to act similarly to arginine and react with  $\alpha$ -dicarbonyls and the imidazolinone moiety to act similarly to guanidine and form Amadori products in the presence of sugars. In the guanidine (HCl)/glucose model (2:5 M) system, however, the intensities of the ions reported in Fig. 1 were diminished and instead high molecular weight ions

were observed. Finally, as shown in Fig. 1, we have also observed the formation of non-covalent dimeric structures of guanidine at  $[M+H]^+ = 119$  and that of its Amadori product at  $[M+H]^+ = 479$  and its further non-covalent interaction with up to three molecules of glucose (Fig. 1 and Table S2). These ions however could be formed during the electrospray ionization process.

### 3.2. Reaction of arginine in the presence of glucose

Under similar reaction conditions of guanidine with glucose, arginine also formed Amadori product at the  $\alpha$ -amino group ( $[M+H]^+ = 337$ ) and imidazolone derivatives with *in-situ* formed 3-deoxyglucosone at  $[M+H]^+ = 319$  and hydroimidazolone with methylglyoxal at  $[M+H]^+ = 251$  (see Fig. 3). In addition, a peak was detected at  $[M+H]^+ = 481$  consistent with the structure generated either from the Amadori rearrangement of ion at  $[M+H]^+ = 319$  or imidazolone formed between the ion at  $[M+H]^+ = 337$  and 3-deoxyglucosone (see Fig. 3 and Table 3). The ion at  $[M+H]^+ = 481$  was only observed in model systems where

glucose was in excess, whereas the ion at  $[M+H]^+ = 319$  was observed in both model systems. Since imidazolones derived from arginine Amadori products have not been reported in the literature, isotope labeling experiments were carried out using  $[^{13}\text{C}-6]$  glucose and the structure of the resulting adduct was studied by MS/MS (see Fig. S1). As expected an ion at  $[M+H]^+ = 483$  was observed incorporating two labeled glucose atoms (see Table 3) and generating four characteristic major fragment ions at  $[M+H]^+ = 465$ , 320, 166 and 112 upon MS/MS analysis. Loss of water generated the peak at  $[M+H]^+ = 465$ , loss of sugar moiety generated peaks at  $[M+H]^+ = 166$  and 320 and finally loss of three molecules of water from the sugar fragment generated the ion at  $[M+H]^+ = 112$  with predicted elemental composition as shown in Table 3. Furthermore, similar to the behavior of guanidine, non-covalent dimeric structure of arginine was also observed at  $[M+H]^+ = 349$  in addition to its further interaction product with four molecules of glucose at  $[M+H]^{2+} = 625$  (see Fig. 3 and Table 3), this ion was mainly observed in model systems where glucose was in excess.

This study has indicated that free arginine can interact with sugar-derived  $\alpha$ -dicarbonyl species such as 3-deoxyglucosone or methylglyoxal under cooking conditions, similar to protein-bound arginine residues (Henle et al., 1994), to form imidazolone derivatives. Similarly, free arginine-Amadori product also forms the corresponding imidazolone derivative with 3-deoxyglucosone.

#### 4. Conflict of interest

The authors declare no competing financial interest.

#### Acknowledgements

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.foodchem.2016.09.173>.

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