Direct Trapping of Acrylamide as a Key Mechanism for Niacin's Inhibitory Activity in Carcinogenic Acrylamide Formation

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The inhibitory mechanism of niacin, which was found in our previous study to effectively reduce acrylamide (AA) formation in both chemical models and fried potato strips, was investigated in the present study. Maillard chemical models containing the amino acid asparagine and glucose with or without niacin were closely examined by liquid chromatography/tandem mass spectrometry. Comparison of the chemical profiles revealed two additional peaks in models where niacin was present together with the AA precursors, which thus suggests the formation of compounds from reactions between niacin and other chemical species in the model systems. The predicted molecular weights of these two analytes were consistent with adducts formed between niacin and asparagine or AA, respectively. The niacin−acrylamide adduct was also detected in fried potato strips pretreated with niacin. In addition, the niacin−acrylamide adduct was subsequently purified and characterized by NMR spectroscopy as 1-propanamide-3-carboxy pyridinium, a novel compound that has never been reported previously. Furthermore, incubation of niacin with AA in simulated physiological conditions showed that niacin was capable of significantly reducing the level of AA. Findings from this study suggest that niacin not only has the potential to remove AA from food products during heat treatment by directly trapping it but also is a potential agent to scavenge AA in human body.

Introduction

Acrylamide (AA) was discovered at unexpectedly high levels in widely comsumed commericial and homemade starchy foods by scientists from Sweden in April 2002 (*1*). This discovery was soon confirmed by multiple international authorities through their survey of locally available foods that contained AA. Because AA has been observed to be carcinogenic in rodents (*2*) and is classified as a probable human carcinogen (*3*), it has raised considerable public concern. In 2009, Health Canada added AA to a list of toxic substances, and some strategies were suggested to reduce dietary exposure to this toxicant (*4*). Immediately after the confirmation of high concentrations of AA in daily consumed foodstuffs in 2002, the European Community (*5*) and WHO (*6*) initiated projects for minimizing the level of AA in various foods. In the meantime, there have been extensive studies on the formation mechanism of AA. The Maillard reaction, the most common reaction during thermal processing of foodstuffs, was found to contribute to AA formation. It has been proposed that AA may be generated from a reaction between asparagine and reactive carbonyls, proceeding through intermediates including Schiff base and some reactive carbonyl species (*7*–*9*). Isotopic studies proved that the nitrogen in AA is derived from the amide group of asparagine. A number of factors, such as heating temperature and time, concentration and ratio of the original reactants, water activity, and pH, etc., have been investigated to understand their effects on AA formation. Among them, temperature seems to be the most important factor affecting AA formation. Thus, low heating temperatures might lead to lower AA levels in foodstuffs. Food additives have been widely studied for their effects on AA formation. Some amino acids such as cysteine, lysine, and glycine were found to be effective inhibitors of AA formation (*10*). Sodium hydrocarbonate, an important constituent of baking powder, has also been reported as an effective inhibitor against AA formation (*11*). Food antioxidants have been reported to modulate AA formation but with widely varying effects. Becalski et al. have shown that the addition of rosemary to frying oil could decrease AA formation in fried potato slices (*12*), and the addition of a flavonoid spice mix that results in relatively lower amounts of AA has also been reported by Fern'andez et al. (*13*). On the other hand, Tareke et al. have found that the pretreatment of meat with antioxidants (butylated hydroxytoluene, sesamol, and vitamin E) enhanced the formation of AA (*14*). Vitamins are important nutritious food additives. Our previous study tested 15 vitamins for their activities against AA formation in Maillard model systems and foodstuffs. Niacin, a water-soluble vitamin, demonstrated potent inhibitory activities against AA production in both chemical model systems and fried potato strips. For fried potato strips treated with a 1% niacin dipping solution, a 50% inhibitory effect was observed (*15*). We also carried out LC-MS quantitative analysis to evaluate the content of niacin in fried pototo strips treated with a 1% niacin dipping solution; preliminary data showed that this special treatment produced fried potato strips with a niacin content of 10−14 mg/100 g of fried potato strips, much higher than the niacin content in regular French fries (2 mg/100 g from the U.S. Department of Agriculture database). However, this treatment still has practical meaning, as the daily recommended value of niacin is 20 mg, and only at a large dosage (500 mg daily) can niacin be toxic.

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Table 1. Aqueous Chemical Model Reactions for Mechanism Study[a]

reactants	A	B	C	D	E	F	G	H
asparagine	1.00	1.00				0.04		0.04
glucose	1.00	1.00						
niacin		0.30	0.04		0.04		0.04	0.04
AA				0.05	0.05			

[a] All of the model reactions were carried out in 2 mL of water and heated at 135 ± 3 °C for 120 min.

There have been many studies that aim to identify effective inhibitors of AA formation. However, studies on the mechanism of action of potential inhibitors are limited. Scavenging of free radicals and reactions with intermediates for AA formation have been proposed to be the AA reduction mechnism by some inhibitors. As examples, Gema et al. have recently reported that pyridoxiamine reduced AA formation probably via scavenging of 3-APA by transferring it into a stable adduct (*16*). Our previous work showed that naringenin, a citrus flavanone, effectively inhibited the formation of AA in a model system via adduct formation with AA precursors/intermediates (*17*). In the present study, a series of experiments were designed to figure out the inhibitory mechanism of niacin, the most effective vitamin type AA formation inhibitor identified in our previous study.

Experimental Procedures

Solvents and Reagents. AA standard (≥99.8%), asparagine, glucose, niacin, and phosphate-buffered saline (PBS, pH 7.4) were purchased from Sigma-Aldrich Co. (St. Louis, MO). All solvents used were of analytical grade and were obtained from BDH Laboratory Supplies (Poole, United Kingdom). Fresh potato and peanut oil were purchased from a local supermarket in Hong Kong. The Reacti-Therm III heating module (model 18840) was purchased from Pierce (Rockford, IL). The food fryer (Philips, HD6157) was purchased from an electric appliances store in Hong Kong.

Model Maillard Reactions. The role of niacin in AA formation was first investigated in chemical model systems. The compositions of different model reactions are listed in Table 1. The reaction mixtures were dissolved in phosphate buffer (0.1 M, pH 7.0, 10 mL) in screw cap Tuf-Bond Teflon-fitted glass reaction vials (40 mL capacity) and heated in a Reacti-Therm III heating module at 135 ± 3 °C. After they were heated, reaction mixtures were immediately cooled down in an ice bath and then prepared for further analysis. For comparison of chemical profiles, reaction mixtures from the asparagine−glucose models with/without niacin (model reactions A and B) were diluted (2×) and subjected to LC-MS analysis after a single syringe-driven filtering step. As for model reactions C−L, 20 μL of the reaction mixture was diluted with 1 mL of water, filtered, and analyzed by LC-MS.

Examination of Niacin−AA Adducts Formed in Fried Potato Strips. Potato strips (10 mm × 10 mm × 60 mm) were prepared and immersed in a 1% solution of niacin for 60 min at room temperature; meanwhile, water was used for immersion of the control samples. The potato strips were drained for 2 min prior to frying, which was carried out in peanut oil at 170 °C for 10 min with an electric fryer (Philips). After they were fried and cooled, the potato strips of each treatment were dipped in 100 mL of hexane to remove oil on the surface. The strips were then ground to a paste, which was then extracted with 100 mL of deionized water by sonication for 60 min. The water extracts of fried potato strips were filtered and evaporated to around 1 mL on a rotary evaporator at 50 °C under vacuum. The concentrated water extracts were then transferred into Eppendorf centrifuge tubes and centrifuged (15000 rpm) for 30 min. The clear supernatant was filtered, and the filtrate was analyzed by LC-MS.

Examination of AA Amounts in Solutions Incubated in Simulated Physiological Conditions. This section of experiments was conducted in a buffer system that simulated physiological conditions: Commercial available PBS in dry powder form was packed in a foil pouch. After the the dry powder was dissolved in 1 L of deionized water, 0.01 M PBS was obtained that contained 0.138 M NaCl and 0.0027 M KCl, pH 7.4, at 25 °C. The buffer (1 mL) solutions containing niacin and AA in molar ratios of 5:1, 10:1, 15:1, and 20:1, respectively, were incubated in a water bath at 37 ± 2 °C. The PBS solution containing only AA was used as a control. The time points were set at 2, 4, and 6 days. At each specific time point, samples were taken out from the incubator and immediately chilled in an ice bath before HPLC analysis of the AA content.

HPLC-UV Analysis. Analytical HPLC was carried out using a Shimadzu LC-20AT system equipped with a diode array detector and LC-Solution software. A prepacked Sunfire C_{18} column (250 mm × 4.6 mm, 5 μm, Waters Corp., Ireland) was selected for analysis of AA. The flow rate was 0.8 mL/min. The mobile phases were water (solvent A) and acetonitrile (solvent B). The elution started with 100% A for 10 min, then a linear gradient to 80% B in 10 min, and finally kept at 80% B for 15 min. The postrunning time was 15 min, and the chromatograms were registered at 205 nm.

Liquid Chromatography−Mass Spectrometry. The samples were analyzed on a LC-MS/MS instrument equipped with an electrospray ionization (ESI) source interfaced to a QTRAP2000 mass spectrometer (Applied Biosystems, Foster City, CA). Liquid chromatography was run on a separation model (Agilent 1100; Agilent Technologies, Santa Clara, CA) with a degasser, a quaternary pump, and a thermostatted autosampler. Separation of Maillard reaction products was conducted on the same Sunfire C_{18} column mentioned above, with the same mobile phase profile at a flow rate of 0.2 mL/min. The elution started with 100% A for 10 min, then linear gradient to 80% B in 20 min, and finally kept at 80% B until 25 min. The postrunning time was 20 min. The MS conditions were as follows: positive mode; capillary temperature, 350 °C; capillary voltage, 4.5 kV; and scan range, 50−600 Da. Collision-induced dissociation spectra were acquired using nitrogen as the collision gas with collision energies of 25 V. The declustering potential was set at 5 V. In enhanced product ion (EPI) mode for niacin−AA adduct detection, $[M + H]^+$ 195 was set for acquisition of the product ion spectra, and in MRM mode for adduct detection in fried potato strips, the reaction product transition *m/z* 195 → *m/z* 72 was set for detection of the adducts in a complex matrix.

Isolation, Purification, and Structural Elucidation of Niacin−AA Adducts. The reaction mixture of niacin and AA was loaded onto an Amberlite XAD-16 column (30 cm × 4 cm i.d.), and elution was performed with water. The eluate was collected in 10 mL fractions whose profiles were checked by HPLC-DAD on a Shimadzu HPLC system. Similar fractions were combined. This open-column chromatographic process eventually led to the target adduct with high purity (over 95% by HPLC). The adduct was characterized by 1D and 2D NMR spectroscopy on a 500 MHz spectrometer (Bruker, AVANCE 500).

Spectral Data of Niacin−AA Adducts. ^{1}H NMR (500 MHz, DMSO-d_6 + D_2O, 25 °C, TMS): δ 9.17 (s, 1H; H-2), 8.88 (d, J = 6.0 Hz, 1H; H-6), 8.82 (d, J = 8.0 Hz, 1H; H-4), 8.07 (dd, J = 6.0 and J = 8.0 Hz, 1H; H-5), 4.86 (t, J = 6.5 Hz, 2H; H-1′), 3.00 (t, J = 6.5 Hz 2H; H-2′). ^{13}C NMR (125 MHz, DMSO-d_6 + D_2O, 25 °C, TMS): δ 174.23 (s, C-3′), 167.38 (s, C-7), 147.11 (d, C-4), 147.06 (d, C-6), 146.98 (d, C-2), 139.74 (s, C-3), 129.50 (d, C-5), 59.16 (t, C-1′), 37.08 (t, C-2′).

Results and Discussion

Niacin Inhibited AA Formation via Direct Trapping of AA in Model Systems. In real food matrices, large numbers of concurrent reactions make it difficult for the analysis of low-abundance chemical species in mechanistic studies. Because of

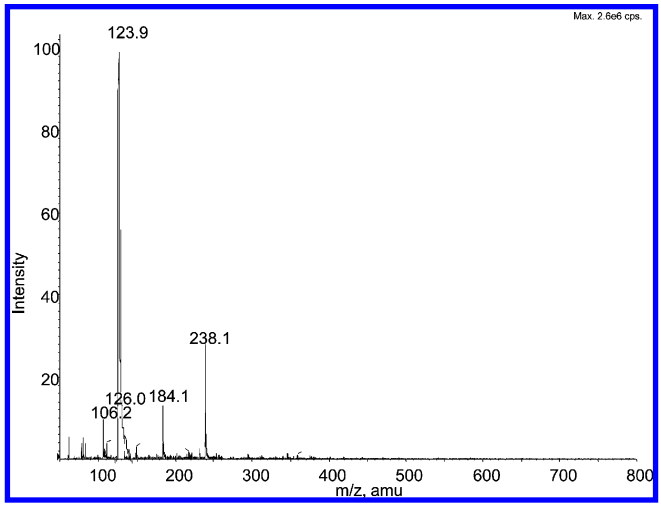

Figure 1. MS spectrum demonstrating the possible existence of niacin−asparagine adducts.

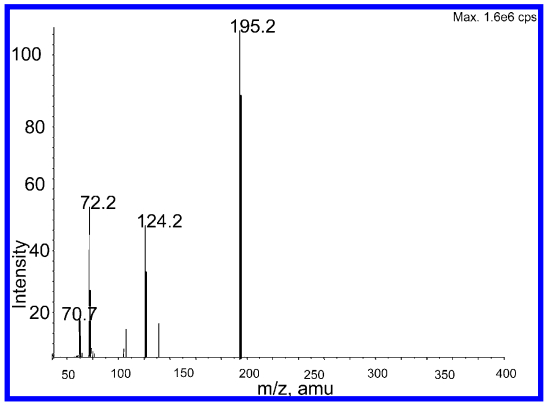

Figure 2. MS spectrum (EPI) of niacin−AA adducts.

this consideration, chemical model reactions that simulate certain aspects of real reactions in food systems have been widely applied in mechanistic studies as these systems can produce higher contents of intermediates and final products. The present mechanistic study thus also started with chemical model reactions to facilitate targeted spectrometric analysis. Initially, asparagine−glucose Maillard model reactions with/without the presence of niacin (models A and B in Table 1) were carried out to identify changes in the chemical profiles of the reaction systems in the presence of niacin. To avoid the loss of potential reaction products of interest, one single syringe-driven filtering step was applied to the reaction mixtures prior to LC-MS analysis. Close examination and comparison of the LC-MS total ion chromatograms revealed two newly formed species in the chemical model reaction with the presence of niacin. One showed a molecular ion peak $[M + H]^+$ at *m/z* 238.1 (Figure 1), which seemed to be a direct combination product of asparagine with niacin, with the elimination of one molecule of water. The other newly formed species showed a huge peak in the total ion chromatogram at *m/z* 195.2, which corresponds to an electrophilic-addition product of niacin to AA at a molar ratio of 1:1. For further confirmation, EPI scan mode was performed to obtain more spectral information of the target peak (Figure 2). It was found that the *m/z* 195.2 precursor ion generated daughter ions of *m/z* 124.2 and 72.2, assignable to the ions arising from the loss of AA and niacin from the parent compound, respectively, suggesting that niacin might directly react with AA.

It was suggested that nucleophiles such as thiols and primary amines might directly trap AA (*18*). Consequently, direct reactions employing niacin and AA (models C−E in Table 1) were carried out at 135 ± 3 °C for 120 min. LC-DAD chromatograms of the model reactions are shown in Figure 3. A new distinct peak was identified at around 17 min in the LC chromatogram of model reaction E. This analyte has a UV absorption spectrum similar to that of niacin (retention time at ∼40 min). In addition, the formation of this compound was found to increase and the level of AA was found to decrease dose dependently with an increasing amount of niacin added to the model system (Figure 4). To investigate the stability of the produced adduct, a time−course study was performed. As shown in Figure 5, the level of the adduct increased with time within the time frame of investigation (60, 120, 180, 300, 360, and 420 min). These data suggested continuous production and accumulation of the target adduct in the chemical model systems. In other words, niacin can be regarded as an effective trapping agent of AA, and such activity is sustainable in prolonged heating processes.

As LC-MS analysis revealed the generation of an adduct (*m/z* 238.1) probably resulting from reaction between niacin and asparagine, in addition to one from niacin and AA (*m/z* 195.2), model reactions (models F−H in Table 1) were carried out to evaluate the relative importance of the second pathway in reducing the AA content in the reaction systems concerned. Surprisingly, no significant change in the level of asparagine was observed in the reaction system containing asparagine and niacin (model H), suggesting that direct trapping of asparagine by niacin is unlikely a major mechanism contributing to the reduction of AA content in AA-producing systems.

Finally, according to Cheng et al. (*17*), scavenging of 3-oxo propanamide might be a possible pathway contributing to naringenin's inhibitory activity against AA formation. If this postulated action mechanism is also applicable to niacin, adduct(s) with *m/z* of 193 should be present in the model systems where niacin and AA precursors are present. Nevertheless, the extract ion chromatogram at *m/z* 193 only revealed a very weak peak signal. Hence, 3-oxo propanamide scavenging is only a minor pathway leading to the inhibition of AA formation by niacin in model systems.

Characterization of the Structure of the Niacin−AA Adduct. To better understand the chemistry of the formation of niacin−AA adducts, the adduct was isolated and purified by chromatographic methods. A higher niacin to AA molar ratio (2.5:1) was used in the reaction because such a ratio was found to favor the generation of the target adduct. The purified adduct was characterized by 1D and 2D NMR spectroscopy. Its ^{13}C NMR spectrum exhibited nine carbon signals, which matched well with a structure of direct addition of one AA to niacin. The presence of a niacin substructure was easily deduced by comparison of its ^1H NMR spectrum with that of niacin. The proton signals at δ 9.17 (s, 1H), 8.88 (d, $J = 6.0$ Hz, 1H), 8.82 (d, $J = 8.0$ Hz, 1H), and 8.07 (dd, $J = 6.0$ Hz and $J = 8.0$ Hz, 1H) clearly indicated the existence of a niacin moiety. The ^1H NMR spectrum also showed signals for a $-CH_2-CH_2-$ moiety at 4.86 (t, $J = 6.5$ Hz, 2H; H-1′) and 3.00 (t, $J = 6.5$ Hz, 2H; H-2′). In the ^{13}C NMR spectrum, the six carbon signals at δ 167.38 (s, C-7), 147.11 (d, C-4), 147.06 (d, C-6), 146.98 (d, C-2), 139.74 (s, C-3), and 129.50 (d, C-5) were assignable to a 3-carboxy-pyridinium inner salt structure, such as the skeleton of trigonelline (*19*). The remaining three signals at 174.23 (s, C-3′), 59.16 (t, C-1′), and 37.08 (t, C-2′) were assignable to a $-CH_2-CH_2-CONH_2$ short chain derived from AA. The full assignment of the structure of this novel adduct was based on the heteronuclear multiple quantum coherence (HMQC) and

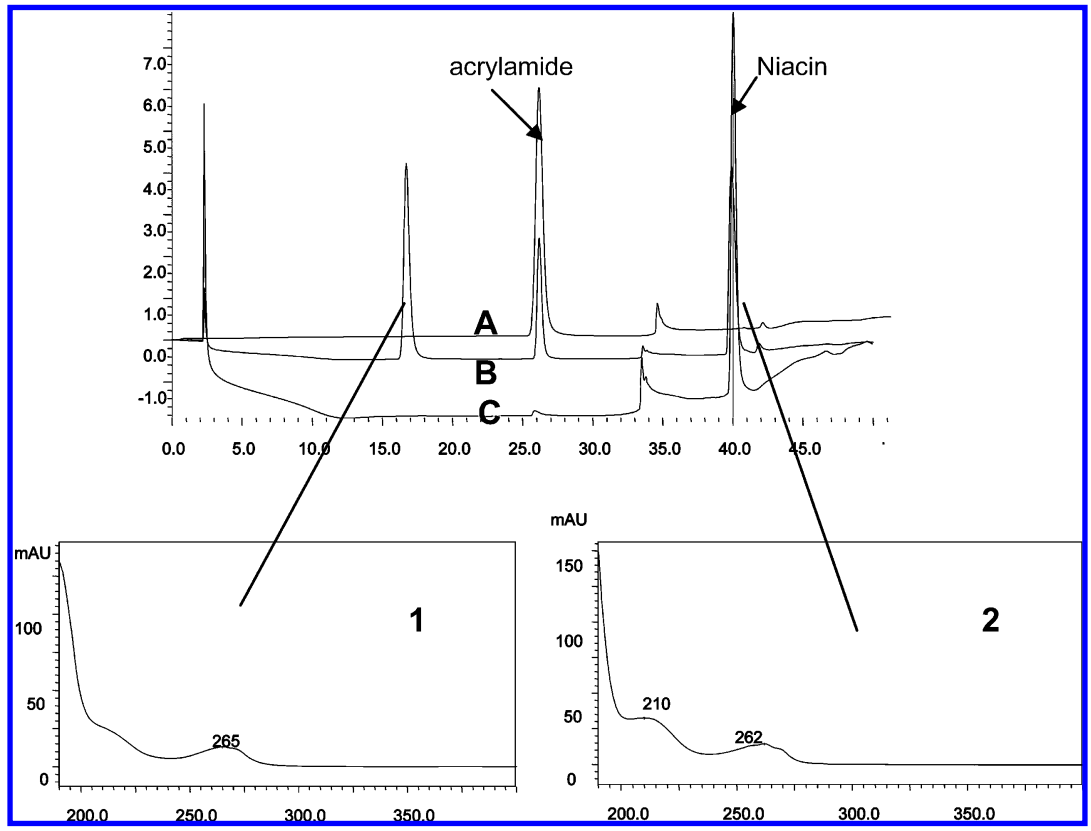

Figure 3. HPLC chromatogram (254 nm) of chemical model reactions carried out at 135 ± 3 °C for 120 min. (A) Model D in Table 1, (B) model E in Table 1, and (C) model C in Table 1. Spectrum 1, UV spectrum of postulated niacin−AA adducts; spectrum 2, UV spectrum of niacin.

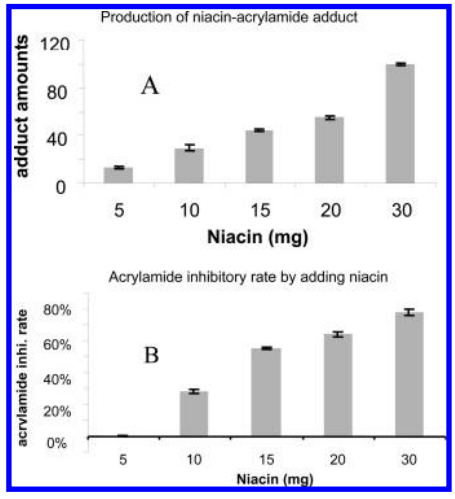

Figure 4. Dose-dependent increase of niacin−AA adducts and decrease of AA in model reactions for niacin directly trapping AA. (A) Amounts of formed niacin−AA adducts with increasing additional amounts of niacin (the amount of niacin−acrylamide adducts produced with the addition of 30 mg of niacin is as 100). (B) AA inhibition rates with increasing additional amounts of niacin.

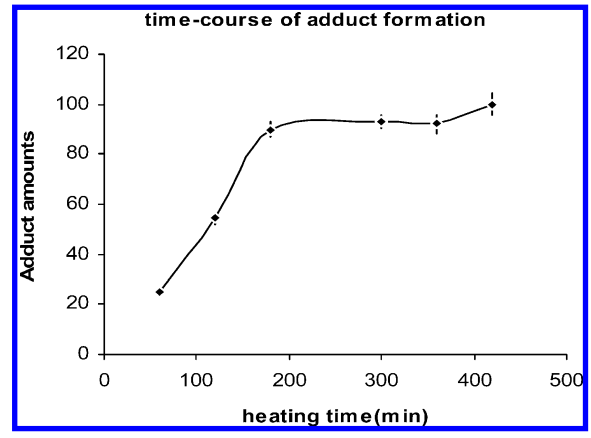

Figure 5. Time course of niacin−AA adduct formation in model reactions.

heteronuclear multiple bond correlation (HMBC) data. The HMQC spectrum supports significant correlations of the following protons to carbons: proton at δ 9.17 to carbon at 146.98, proton at 8.88 to carbon at 147.06, and proton at 8.82 to carbon at 147.11. The HMBC spectrum revealed three-bond couplings of C-1′ to H-2 and H-6 and that of H-4 to C-6 and C-7 as well as double-bond couplings of H-2′ to C-1′ and C-3′. Key HMBC correlations are indicated in Figure 6. The new derivative is thus elucidated as 1-propanamide-3-carboxy pyridinium.

Identification of Niacin−AA Adducts Formed in Fried Potato Strips. Although Maillard chemical model systems consisting of primary AA precursors are considered good surrogates for studying different aspects of undesirable Maillard reaction products, some studies (including ours) also showed that certain chemical agents might exhibit very different performances in chemical models relative to real food systems. Therefore, to test the relevance of the aforementioned mechanism of action (direct AA scavenging by niacin) in real food systems, fried potato strips were prepared for the identification of the adducts of interest. As previous chemical model and reverse-phase HPLC analyses showed that the adduct has a highly hydrophilic property, water was used for its extraction from the fried potato strip samples. This was followed by a series of cleaning and concentration steps before LC-MS/MS analysis. Considering the fact that the adduct was present at low concentrations and in a complex sample matrix, MRM-IDA (multiple reaction monitoring−information-dependent acquisition) mode was applied for its detection. MRM-IDA consists of an MRM survey scan, and if a signal of interest is

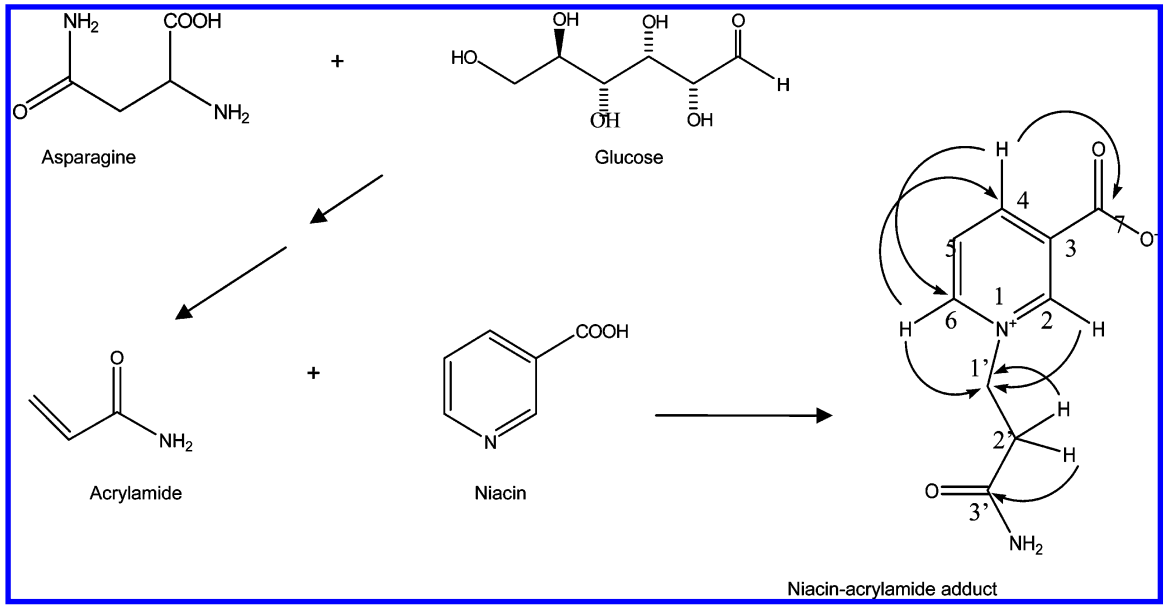

Figure 6. Summary of the inhibitory mechanism of niacin for AA scavenging and key HMBC correlations of purified niacin−AA adducts.

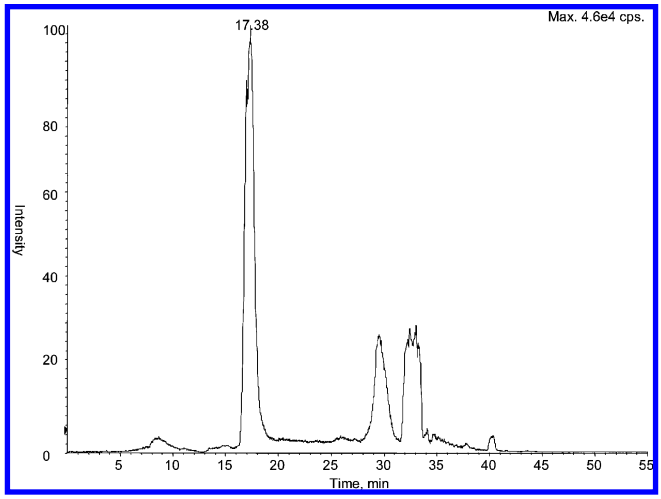

Figure 7. Niacin−AA adduct detection (RT = 17.38 min) by LC-MS/MS (MRM mode) in the water extract of fried potato strips.

detected, EPI MS-MS spectrum acquisition follows. As shown in Figure 7, the target peak has a similar retention time as the purified adduct. Its MS-MS spectrum was similar to that of the *m*/*z* 195.2 adduct ion identified in chemical model reactions (Figure 2) with *m*/*z* 124.2 and 72.2 as the dominant product ions. These spectral data suggested that the proposed adduct formation reaction (electrophilic substitution) did take place in the fried potato strips. The fried potato model employed in the present study together with the simple sample preparation methods may be adopted by further studies to investigate mechanisms of reduction of AA content in food matrices.

AA Trapping Capability of Niacin in Simulated Physiological Conditions. Although many chemical agents and natural products have been reported to be capable of inhibiting AA formation in food products, complete removal of AA from food remains a challenge for the food industry. Therefore, human bodies are still susceptible to exposure to AA upon the consumption of high-temperature-processed carbohydrate-rich foods. In this regard, chemical agents capable of directly scavenging AA in physiological conditions would be of considerable significance. Consequently, the AA trapping activity of niacin in simulated physiological conditions was studied.

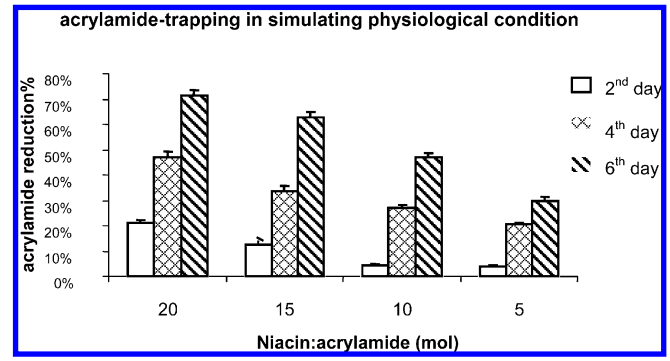

Figure 8. Activity of niacin in direct trapping of AA in simulated physiological conditions.

As shown in Figure 8, levels of AA were reduced in systems where niacin was present, and the extent of reduction was greater when a higher niacin to AA molar ratio was used and so was a longer incubation time. For example, after AA was incubated with niacin (niacin:AA, 20:1, molar ratio) for 2 days in simulated physiological conditions, the AA content was reduced by 21%, while incubation for 6 days in the same molar ratio resulted in 71% reduction. These data suggested the AA trapping potential of niacin in simulated physiological conditions.

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