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Glycation Reactions

Baking, Ageing, Diabetes: A Short History of the Maillard Reaction

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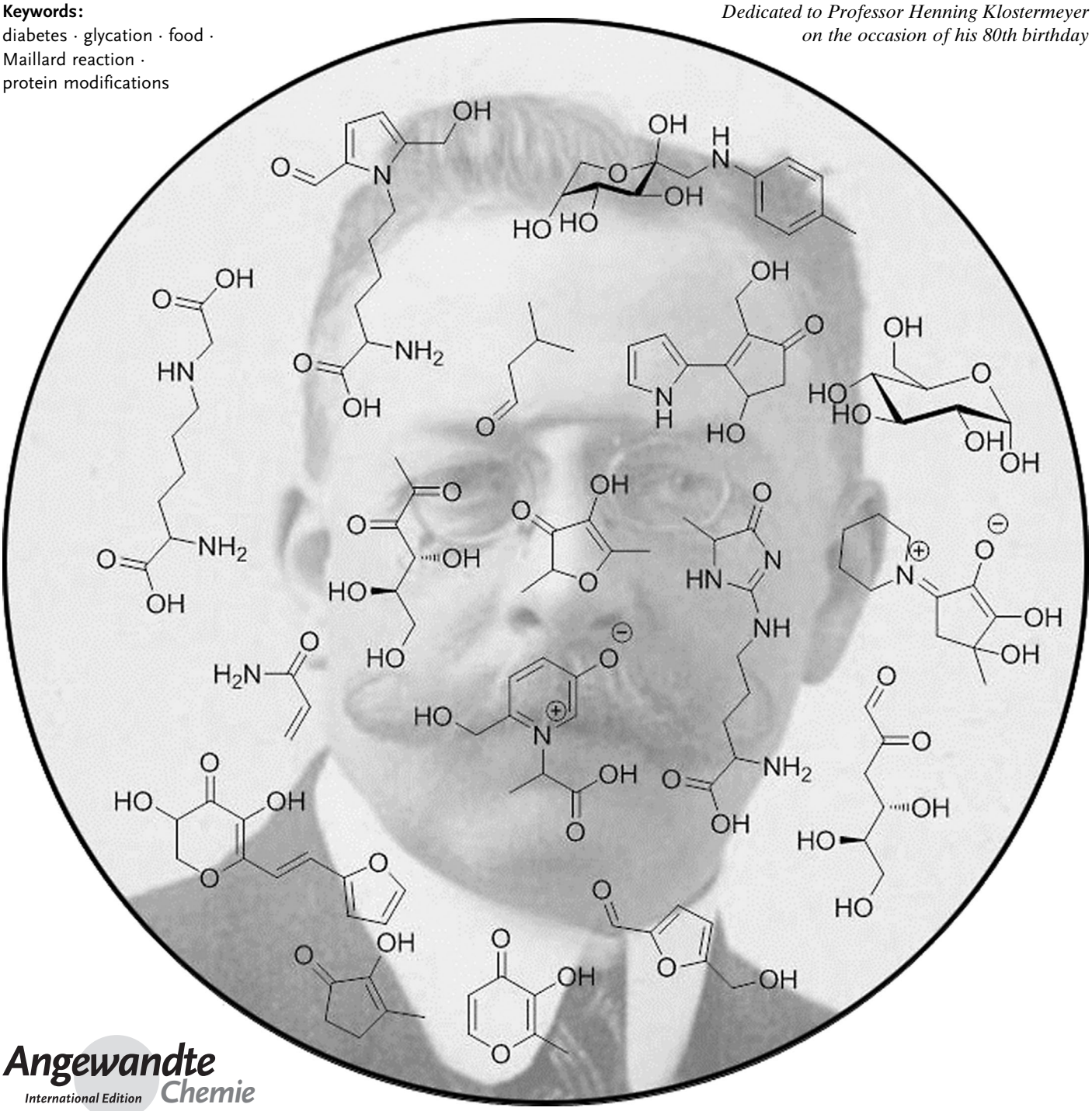
diabetes · glycation · food · Maillard reaction · protein modifications

Dedicated to Professor Henning Klostermeyer on the occasion of his 80th birthday



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The reaction of reducing carbohydrates with amino compounds described in 1912 by Louis-Camille Maillard is responsible for the aroma, taste, and appearance of thermally processed food. The discovery that non-enzymatic conversions also occur in organisms led to intensive investigation of the pathophysiological significance of the Maillard reaction in diabetes and ageing processes. Dietary Maillard products are discussed as "glycotoxins" and thus as a nutritional risk, but also increasingly with regard to positive effects in the human body. In this Review we give an overview of the most important discoveries in Maillard research since it was first described and show that the complex reaction, even after over one hundred years, has lost none of its interdisciplinary actuality.

From the Contents

1. Introduction

Louis-Camille Maillard (1878–1936) discovered in 1912, rather by chance, that mixtures of amino acids and sugars become intensively brown upon heating.[1] He thus laid the basis for understanding the non-enzymatic browning reactions occurring during cooking, roasting, and baking of foods, which until then had only been speculated upon.[2,3] After over 100 years of research, over 50 000 scientific publications, and 11 international symposia on the Maillard reaction, this Review will focus more on the history of research on the Maillard reaction than on its chemistry. There are numerous review articles about singular aspects of the Maillard reaction, be it chemical,[4–11] food technological,[12,13] physiological,[8,14–16] or also historically orientated,[15,17,18] and this Review does not claim to be historically complete. Rather, in a historically based survey, this Review will attempt to explain the phases and tendencies of Maillard research over the last 100 years through the respective key aspects of research and to describe how and when answers to central scientific questions were obtained. We still adhere to the established classification of the Maillard reaction in different stages ("early", "advanced", and "final" phase), which—as presented in the following—are each distinguished by characteristic reaction products. We recognise that the history of the Maillard reaction can also be classified in consecutively and parallely emerging, and proceeding phases and "movements"—and also that the complex reaction has today lost none of its relevance after a hundred years since its discovery.

2. First Phase: Maillard Reaction—Unde Venis?

2.1. Maillard and "His" Reaction

At the beginning of the 20th century Emil Fischer succeeded in synthesizing a dipeptide for the first time.[19] Procedures were subsequently devised to couple amino acids into linear peptides. The activation necessary for this, however, required relatively drastic chemical conditions. The French biochemist Louis-Camille Maillard looked for alternative routes which could also occur in physiological systems, and thus was one of the first to investigate protein biosynthesis. Maillard was born in Pont-à-Mousson in north-east France on 04.02.1878 and studied medicine and natural sciences in Nancy.[17] During his work on his second doctorate, he heated various amino acids with glycerol and ascertained that peptides were, indeed, formed. He postulated that the reactions proceeding at 170 °C could even be catalyzed enzymatically in vivo, with amino acid esters of glycerol being formed as intermediates.[20] In a further set of experiments, Maillard used glucose as the polyalcohol instead of glycerol, but the expected peptides were not formed. In fact, the reaction ran completely unexpectedly as a result of the reactivity of the aldehyde groups: the reaction mixture turned brown upon heating for a short period of time and carbon dioxide was formed.[1] Maillard observed that the reaction is not limited to glycine and glucose, but also that other amino acids, peptides, peptones, and sugars react in the same way, albeit to various degrees.[21] In particular, there were considerable differences in the reactivity of individual sugars. Pentoses reacted more quickly than hexoses, and hexoses more quickly than disaccharides. Saccharose did not react at all.[21] After Maillard had carried out the incubation experiments in various gaseous atmospheres (O_2, N_2, H_2), he ascribed the formation of CO_2 to the decarboxylation of the amino acid. However, he was unable to isolate any defined structures from the reaction mixtures.[21]

Maillard's findings were, in so far, fundamental, as starting compounds such as amino acids and sugars were now identified which could react with each other practically

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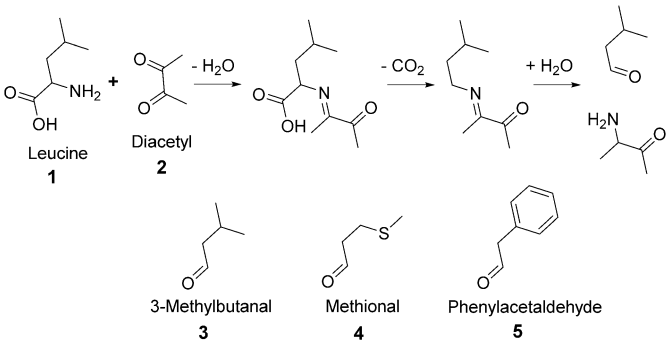
everywhere in nature because of their wide distribution, as Maillard had already postulated, "*not only in human physiology and pathology, but also in plant physiology, agronomics and geology*".[1] However, of Maillard's publications, which number over 100, only eight are concerned with the browning reaction.[17] Maillard took part in the first world war voluntarily and suffered badly from the consequences of a paratyphus infection, which clearly limited his scientific proficiency. After his transfer to the University of Algiers, he did not carry out any further investigations on the non-enzymatic browning reaction. Maillard died on 12.05.1936 in Paris.[17]

2.2 Scientific Reception of the Discoveries of Maillard

In contrast to general opinion, the significance of Maillard's discoveries was perceived and discussed by other researchers directly after their publication. Thus, Maillard's observations[1] provided contributions to understand the formation of the so-called "melanoidins": He attributed the browning[22] observed upon acid hydrolysis to the reaction of amino acids with sugars. This melanoidin formation was ascribed to the degradation reactions of tryptophan.[23] Maillard assumed that reactions of amino acids with sugars were also fundamental for the generation of brown substances in the formation of humus.[21] This viewpoint was criticized early on by contemporaries of Maillard[24] and today is deemed outdated, as Maillard had not incorporated, for example, microbiological processes or the role of lignin and quinone condensation in his considerations.[25]

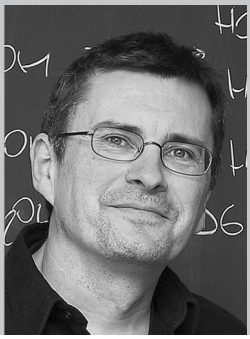
Interestingly, Maillard had not mentioned foods in his discussion on the significance of "his" reaction.[1,21] A contemporary of Maillard, C. J. Lintner from the fermentation laboratory of the former Royal Technical University of Munich, accredited the reaction between amino acids and sugars to have a great technical importance in kilning and brewing processes and to aroma formation.[26] Lintner's co-worker Ruckdeschel postulated that during "Maillard's reaction" the malt aroma is formed mainly by conversions of the amino acid leucine.[27] In this context, Akabori[28] discovered in 1927 that aldehydes were formed in high yield upon decarboxylation of amino acids in the presence of glucose. Other carbonyl compounds such as glyoxal, methylglyoxal, or diacetyl likewise led to the formation of aldehydes.[29] Akabori doubted that glucose remained unchanged in this reaction, but did not carry out any systematic studies on this.[30] Schönberg and Moubacher first showed that, for aldehyde formation, *vic*-dicarbonyl compounds are always necessary, which arise as intermediates during the Maillard reaction.[31] This decomposition reaction has been known since 1948 as the "Strecker degradation", after the discoverer Adolph Strecker.[31] The postulate of Ruckdeschel was thus confirmed, as 3-methylbutanal is formed from leucine during the Strecker degradation (Scheme 1); 3-methylbutanal is an important flavoring agent in malt.[32]



Scheme 1. Strecker degradation of amino acids and examples of Strecker aldehydes in foods.

2.3. Amino-Carbonyl Reaction and Amadori Rearrangement

Independently from research on the browning reaction of Maillard, the Italian chemist Mario Amadori attempted in the 1920s to reproduce older works[33,34] on experiments on the condensation reactions of aromatic amines with glucose.[35] Thus, he obtained, for example, a further "labile product" for *p*-toluidine in addition to an earlier described "stable product".[33,34] Amadori assigned the structure of an *N*-glucoside to the labile product and that of a Schiff base to the stable product.[35] The structure of the labile product was confirmed by the research group of the Austrian-German Nobel prize winner Richard Kuhn,[36] but not that of the stable product. Firstly, the stability of the compound in the presence of acids spoke against the classification as a Schiff base, and secondly a mannitolamine was formed instead of a glucitol-



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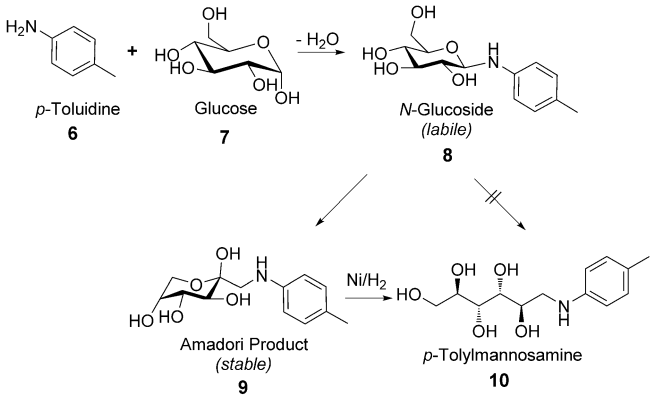
amine during hydrogenation, so that a rearrangement of the sugar residue must have taken place (Scheme 2).[37] This reaction behavior differentiates α-hydroxyaldehydes, to which the aldoses belong, from common aldehydes. The rearrangement of the labile *N*-glycosides was named by Kuhn and Weygand as the "Amadori rearrangement" and the 1-amino-1-deoxy-2-ketoses were later designated as "Amadori products".



Scheme 2. Rearrangement of *p*-tolyl-*N*-glucoside to the Amadori product.

The results could be transferred to the reaction of carbohydrates with α-amino acids in foods. For example, it was determined by using polarimetry and cryoscopy that the reaction of a sugar with the free amino groups of aliphatic amino acids proceeds in a ratio of 1:1 and is accelerated in alkaline conditions.[38,39] However, for a long time it was not possible to isolate the corresponding reaction products, and so the viewpoint prevailed until 1951 that the Amadori rearrangement was limited to *N*-glycosides of aromatic amines.[5,40] The Amadori products of aliphatic amines or amino acids important in foods were first made available in the 1950s.[41,42] Both isomers of fructoselysine (*N*-α- und *N*-ε-fructoselysine), which are very important for protein chemistry, were isolated for the first time in 1962 by using ion-exchange chromatography.[43]

Kurt Heyns, a chemist at the Chemical Institute of the University of Hamburg, observed the formation of D-glucosamine in the reaction of fructose with ammonia.[44] Shortly afterwards, the reaction pathway was transferred to derivatives of aliphatic amines and amino acids by Carson[45] and also by Heyns et al.[46] The formation of aldose derivatives from amino acids and ketoses in an analogous way to the Amadori rearrangement is known today as the Heyns rearrangement. The Amadori and Heyns rearrangements also have preparative significance.[47]

3. Second Phase—The Maillard Reaction in Foods

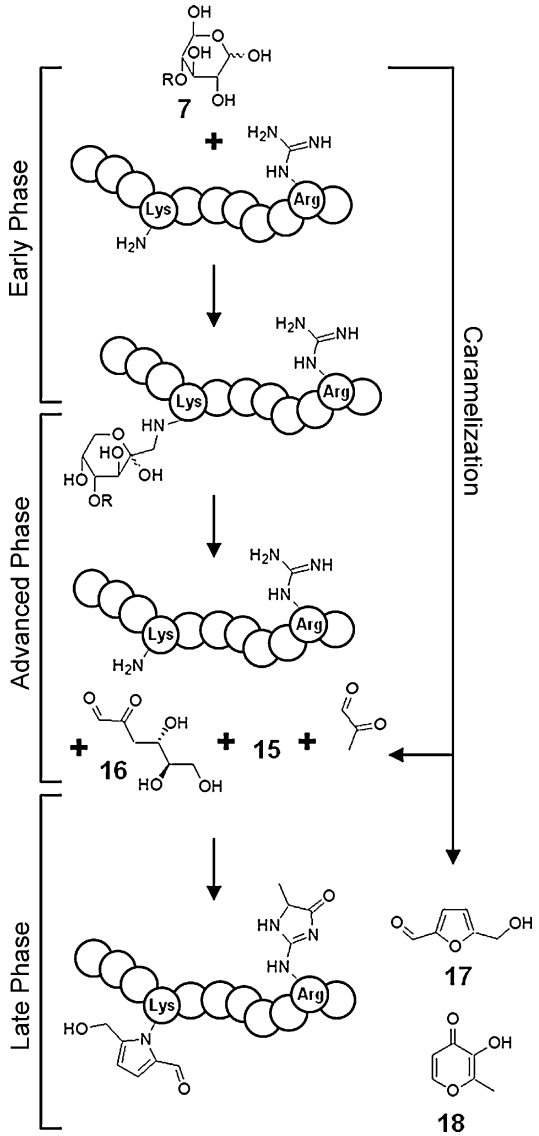
3.1 Browning—Desired or Not Desired

Into the 1940s, only selective attempts were made to describe the significance of the Maillard reaction for the chemical changes occurring during the manufacture, processing, and storage of foods. During the second world war, the need for nonperishable dried or heat-treated foods increased dramatically and thus so did the interest in the browning reaction.[48,49] The description "Maillard reaction" has been used without a reference in the food chemistry literature since the 1940s.[49,50] Particularly in industry, there was a strong interest in inhibiting undesired browning reactions, for example, in dried fruit or milk powder.[51] In such products, the water activity was recognized as the determining factor in the reaction process.[52] Action was taken thereafter to preserve the nutritional value of food. The drum drying of milk for the manufacture of milk powder, for example, lost its importance to a large extent. Only recently has the Maillard reaction been used specifically to influence the functionality of proteins in foods for technical applications.[13]

The dispute whether the first stable products of the Maillard reaction in foods are glycosylamines or Amadori products[5,53,54] was first resolved at the beginning of the 1950s in favor of the Amadori products, after they were independently synthesized.[41,55] On the basis of this, John E. Hodge, a chemist at the Northern Regional Research Institute in Peoria (Illinois, USA), presented a comprehensive description of the reaction in the first volume of the *Journal of Agricultural and Food Chemistry* in 1953, which even now remains fundamental. Hodge accredited the Amadori rearrangement with a key role in the reaction and divided the reaction into an early phase (formation of the Amadori products), an advanced phase (degradation of the Amadori products), and a late phase (formation of melanoidins; Scheme 3).[6] He succeeded in identifying the similarities of several reaction paths (amino-carbonyl reactions, caramelization, oxidative reactions) and uniting them as "partial mechanisms" in a single browning reaction. Hodge explained the catalytic role[41,56] of the amines in sugar degradation by the formation and the subsequent degradation of the Amadori products. Here the amine emerges initially unchanged, but can later undergo a reaction with the sugar degradation products, for example the Strecker degradation products.

3.2 Degradation of the Amadori Products and Aroma Formation

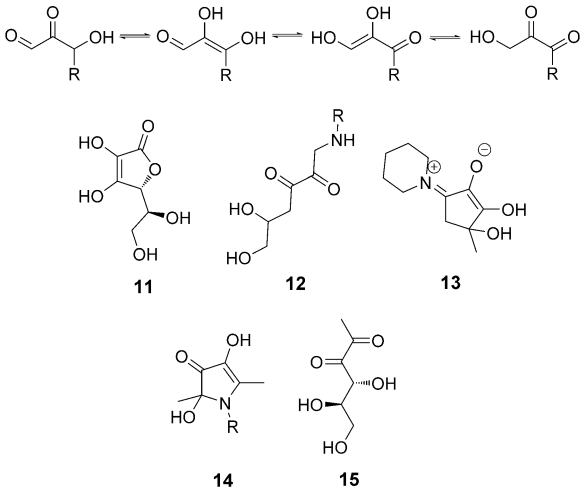
On the basis of the review by Hodge[6], many investigations were carried out on the degradation of the Amadori products. From the 1950s to the 1970s two important fields of research formed, one to explain the blockage of lysine and one to investigate aroma formation. While at first the description of the abundance of products was paramount,[57] the individual reaction pathways were later more exactly considered and analyzed under food-relevant conditions.[58,59] *vic*-Dicarbonyl compounds were identified as key compounds in the degradation of the Amadori products, in particular



Scheme 3. Maillard reaction on proteins.

those with a reductone structure (α-ketoenediol structure, cf. ascorbic acid **11**).[7,55,60] Reductones such as **12** and **13** can form directly from Amadori products, while the pyrrolinone derivates **14** arise from primary amines by reaction with the sugar degradation product 1-deoxyglucodiulose (1-DG, **15**).[61,62] The ease by which the reductones can be oxidized can explain some of the antioxidative properties of melanoidins (Scheme 4).[63]

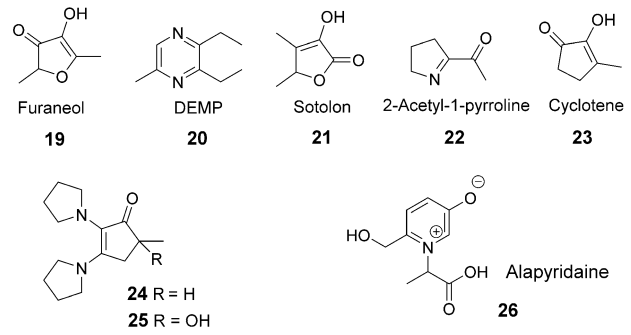
In the pH range important for food, the degradation proceeds in several ways via characteristic compounds with two vicinal carbonyl groups (*vic*-dicarbonyl compounds) as intermediates.[8] The most important quantitative compound here is 3-deoxyglucosone (3-DG, **16**; Scheme 3), which had already been postulated in sugar degradation reactions by Wolfrom et al.[56] and was first isolated and characterized by Anet in 1960.[60] Thus, it was recognized that hydroxymethylfurfural (HMF, **17**) does not form directly on the protein but only after release of the precursor 3-DG. It was only in the 1980s that a reliable quantification of *vic*-dicarbonyl com-



Scheme 4. Reductones in foods and model reaction systems. Tautomeric structures and relevant compounds.

pounds such as **12** and **15** was set up when Moree-Testa and Saint-Jalm adopted the known formation of quinoxalines from dicarbonyl compounds and *o*-phenylenediamine for the analysis of these products in cigarette smoke.[64] This method of derivatization has since then been used to explain the reaction pathways in the degradation of sugars[65–67] and employed in the analysis of compounds in food and physiological media.[68,69] The *vic*-dicarbonyl compounds can fragment into short-chain carboxylic acids as well as carbonyl and dicarbonyl compounds, which themselves can be aroma-active, such as diacetyl (**2**) which smells like butter. However, more important than their contribution to aroma is their role in the Strecker degradation. Furthermore, homo- and heterocyclic compounds that are important for flavoring form from *vic*-dicarbonyl compounds: pyrazines, pyranones such as maltol (**18**), furans, furanones, pyrroles, and sulfur-containing compounds such as thiophenes and thiazoles.[70] The aroma of individual heated foods can, however, never be sufficiently imitated by one flavoring substance alone. To analyze the aroma profile, in the 1980s gas chromatography was coupled to olfactometry (GC-O),[71] whereby the GC effluent is "sniffed". This method was used, for example, by the Grosch research group at the Deutsche Forschungsanstalt für Lebensmittelchemie in Garching to prove that the strawberry-like smelling furaneol (**19**), the pyrazine DEMP (**20**) and methional (**4**) in meat roasts[72], and sotolon (**21**) and 2-ethyl-3,5-dimethylpyrazine in roasted coffee[73] were compounds resulting from the Maillard reaction and have a strong influence on the aroma (Scheme 5). Interestingly, the "strawberry note" in wine was also attributed to furaneol.[74] The most important flavor compound in the crust of white bread is 2-acetyl-1-pyrroline (**22**; popcorn aroma).[75] Typical caramel aromas which also occur in the absence of amines are attributed to furaneol (**19**) und cyclotene (**23**).[76]

In addition to these desired aromas, the research group of Belitz at the TU Munich showed that off-flavors are also formed during the Maillard reaction, such as bitter substances, for example the substituted aminohexose reductones **24**



Scheme 5. Aroma and taste-active compounds resulting during the Maillard reaction or caramelization.

and **25** isolated from "roasted" proline/saccharose mixtures.[77] More recently, the Maillard product alapyridaine (**26**) was described, which acts as an enhancer for a variety of different tastes.[78]

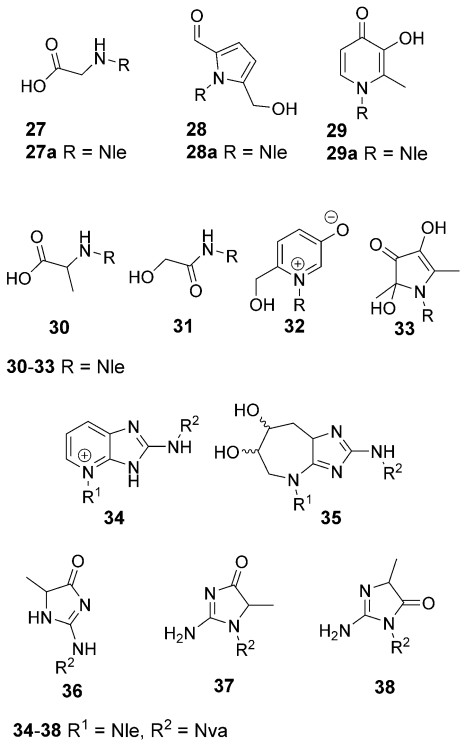
The highly reactive intermediates formed in the advanced phase react to form stable end products in the final phase of the reaction. The target for the very electrophilic dicarbonyl compounds are again free amino groups. Particularly important reaction pathways, besides the formation of the Amadori product and the Strecker degradation, are the formation of N-carboxyalkylated amino acids **27** and N-heterocyclic systems (for example, **28** and **29**),[79,80] which result from reactions with *vic*-dicarbonyl compounds (Scheme 6). Similar to caramelization,[81] specific products result, such as the pyridinones **29**, in the presence of disaccharides (Table 1).[82]

Interest in the formation of protein-bound Maillard products in food increased when the Maillard reaction was more intensively investigated in the human body at the beginning of the 1980s (see Section 4). Here, the reactions on the N terminus become less important and the nucleophilic side chains of amino acids, in particular the ε-amino group of

Table 1: Content of selected Maillard reaction products in foods.

Food	ARP[83,84] [g kg^{-1}][a]	CML[85,86] [mg kg^{-1}]	Pyrraline[87] [mg kg^{-1}]	Pentosidine[88] [mg kg^{-1}]	AGE[89] [MU/kg]
milk, pasteurized	ca. 0.1	0.2–0.5	n.d.	n.d.	0.01–00.1[b]
evaporated milk	7–18	46	0.4–3.2	0.02–0.04	–
pasta	1–19	2.4–3.0	n.d.–12	–	–
bread	6–7	3–40	6–69	–	1.1–1.5
bread crusts	–	37–46	60–240	0.03–0.18	0.4–0.7
meat, roasted	–	2–20	–	–	47–100
butter	–	0.3–0.4	–	–	233–265
coffee, roasted	–	–	–	1.0–4.0	–

[a] Amadori product calculated as fructoselysine. [b] Type of heat treatment not given. n.d.: not detectable, –: no value available.



Scheme 6. Structures of selected products of the advanced Maillard reaction (advanced glycation end products). Nle = norleucine, Nva = norvaline.

lysine and the guanidino side chain of arginine, react primarily. However, the reactivity of individual proteins is dependent on the amino acid composition, the primary, secondary, and tertiary structure, and particularly on the presence of cysteine.[90] The term "advanced glycation end products" (AGEs) was coined for these amino acid derivatives which accumulate on proteins.[91] The first confirmed structure was pyrraline (**28a**),[92] which results from the reaction of lysine residues with 3-DG. Later came carboxymethyl- (**27a**)[93] and carboxyethyllysine (**30**),[94] amides **31**,[95] pyridinium betaines of the type **32**,[96] and pronyllysine (**33**).[97] The glycation of amino groups in aminophospholipids (phosphatidylethanolamine and -serine) leads to similar products.[98,99] The AGEs include the cross-linked products pentosidine (**34**)[100] and glucosepan (**35**).[101] Protein-bound arginine reacts with 1,2-dicarbonyl compounds to give mostly hydroimidazolones (Scheme 6). The blockage of arginine with cyclohexanedione was used in the 1960s to generate longer or overlapping peptides upon tryptic hydrolysis of proteins.[102] The analogous compound MG-H1 from methylglyoxal (**36**) was first described in 1994 and detected in food.[103] Beyond the δ-N exocyclic structure **36,** the compounds MG-H2 (**37**) and MG-H3 (**38**) can also occur if the dicarbonyl compound attacks the δ-N atom of arginine. These structures also result analogously from other 1,2-dicarbonyl compounds.

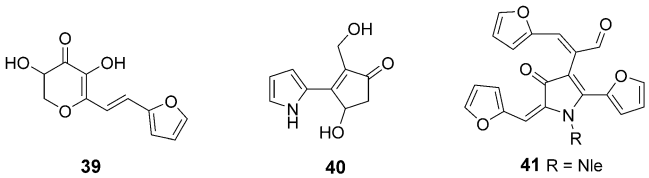
In case the amine bond remains intact, several of the compounds stated above also form directly by degradation of the Amadori product. Reductone structures such as **12** can be

generated in this way. In such structures, migration of the carbonyl group through the complete sugar residue has been described, which can be attributed to consecutive keto-enol tautomerizations.[104] CML (**27a**) can form either from the Schiff base ("Namiki pathway")[105] or by Baeyer–Villiger oxidation of Amadori products.[106] Differences in the browning activity of the Amadori products were attributed to the different stability of the cyclic forms, which are critically influenced by the substitution at the C-4 position.[107]

Many of the amino acids glycated on the side chain have since then been detected in food by using chromatographic methods (Table 1). In a typical "Western diet", about 1000 mg of Amadori products and 25–75 mg AGEs, mainly **27a** and **28a**, are ingested daily by humans.[108] In addition to chromatographic analysis, immunological methods are also being employed to quantify AGEs in food.[89] Thus, by using an enzyme-linked immunosorbent assay (ELISA), which should primarily detect CML, values were determined which are in stark contrast to results which are obtained from structure-based analytical methods (Table 1). Interestingly, the CML content measured by the ELISA method correlates better with the fat than with the carbohydrate content,[109] which throws up serious doubts on the specificity of the antibody and the identity of the measured structures.

3.3. Melanoidins

Maillard created the term "melanoidins" and postulated a heterocyclic character for the structure of the brown to black end products of the reaction. The first insights into the composition of the melanoidins were made from pyrolysis and photometric studies, from which the presence of pyridine, pyrrole, and furan rings was concluded.[4,56] Attempts were then made to derive a defined structure from calculation of the empirical formulas and molecular masses.[48] Molecular weights of 1000 to 2000 Da were initially expected for the melanoidins,[4] which were corrected to significantly higher values after analysis by gel-permeation chromatography.[110] Today, masses well above 100 kDa are assumed.[111] Structural characterization of the melanoidins is made more difficult as other constituents of the food matrix can also be incorporated into the structure, in particular phenolic substances.[111] Proof of defined functional groups was first achieved in the 1980s by using two-dimensional NMR spectroscopy.[112] It is currently assumed that dehydration and condensation of carbohydrates account for the color of the melanoidins, and that these aggregates are bound to proteins through nucleophilic groups.[113] It is also postulated that repeating structural units occur, particularly with furan and pyrrole cores, but these have only been described in model systems.[114,115] Thus, nucleophilic amino acid side chains on proteins, N termini, and also the protein backbone are presumed to represent "nuclei" on which these repeating units can group. In the 1980s, the isolation of increasingly more complex adducts from the Maillard reaction mixtures led to the synthesis of defined colored compounds, such as **39** and **40** (Scheme 7),[116,117] which could represent the basic building blocks of higher polymeric melanoidins. In 1998, the furfural



39 **40** **41** R = Nle

Scheme 7. Colored compounds isolated from model systems.

addition product **41** was the first protein-bound, colored lysine derivative to be isolated.[118]

3.4. Nutritional Evaluation of the Maillard Reaction

The fact that the biological value of skimmed milk powder is reduced by heating has been known for a long time.[119] However, it was only in feeding experiments in the 1930s that it was first realized that the loss of nutritional value could be compensated by the addition of the essential amino acid lysine or intact proteins.[120,121] The heat-induced deterioration of skimmed milk powder was first attributed by Henry et al. to the Maillard reaction and the associated irreversible modification of lysine residues.[50] At the same time, it was noted that beyond lysine other proteinogenic amino acids such as arginine, tryptophan, and methionine, were also degraded during the reaction with sugars.[122,123] The poor utilization of heat-damaged proteins can partly be explained by a reduced digestibility.[124,125] However, it is also worth mentioning that the nutritional value of proteins can be improved by heating, if, for example, enzyme inhibitors are inactivated or the digestibility is improved by denaturation.[124,126]

As a consequence of the significant role of the essential amino acid lysine for the nutritional value of proteins, chemical methods were subsequently established to investigate the lysine blockage. Thus, 1-fluoro-2,4-dinitrobenzene[127] (Sanger reagent), which was originally applied at the end of the 1950s to determine N-terminal amino acids in polypeptide chains, was used to determine the chemically reactive and thus "available" protein-bound lysine.[128] The fraction of blocked lysine could be indirectly estimated when the lysine starting content was known.[129] A direct measurement of lysine blockage was only possible at the end of the 1960s after the discovery of furosine.[130,131] Fructoselysine and other food-relevant Amadori products of lysine, such as lactuloselysine and maltuloselysine, are converted into reproducible amounts of the products furosine, pyridosine, and CML under acid hydrolysis conditions; in addition, lysine is also regenerated.[132,133] With furosine, a parameter was available for the first time which allowed the Amadori products of lysine to be determined. Furosine has since then been used as a quality parameter for manufactured foods.[83,134] The α-amino groups of free amino acids, the N-termini of polypeptides, and also proteins react similarly as quickly to the Amadori products as the ε-amino group of lysine,[135] but quantitatively they are not that important. These Amadori products are converted analogously into *N*-(2-furoylmethyl)amino acids by acid hydrolysis.[131] The

amounts of Heyns products in foodstuffs have not yet been published. Furthermore, comparatively little is known about the role of Heyns products in glycation events in vitro and in vivo.

4. Third Phase—The Maillard Reaction In Vivo

4.1 Glycation of Hemoglobin

Maillard had already recognized that "his" reaction between glycine and glucose also occurred at 37 °C and that—after sufficient incubation times—the analogous reaction products are ultimately formed as those obtained by strong heating. A possible significance of the reaction in physiological processes was subsequently discussed thoroughly.[4,39] However, effective analytical methods for the conclusive proof of an in vivo on-going Maillard reaction were first needed. In 1955, an unknown variant of human hemoglobin was described in electrophoretic investigations of the blood protein,[136] which Samuel Rahbar at the Albert Einstein College of Medicine in New York linked to *Diabetes mellitus* for the first time in 1968.[137] In this haemoglobin variant, which was later designated as HbA_{1C}, the N-terminal valine residue of the β chain exists as an Amadori product, formed from the non-enzymatic conversion with glucose, as known in food.[138,139] Today, the HbA_{1C} value is used as an important parameter in clinical chemistry to retrospectively assess the average blood-glucose concentration of diabetic patients.[140] The elucidation of the structure of HbA_{1C} formed the beginning of investigations on the Maillard reaction in physiological systems. The term "non-enzymatic glycosylation" was first, then later "glycation", given to this. As a result of its interdisciplinary significance, symposia dedicated to the Maillard reaction have been held regularly since 1979. Since 2005, these have been organized by the International Maillard Reaction Society (IMARS).

A feature of the glycation in vivo is the occurrence of highly reactive metabolic intermediates such as glycerinaldehyde-3-phosphate and dihydroxyacetone phosphate.[141] In particular, numerous AGEs such as CML[93] and pentosidine[100] can be detected on proteins with a low "turnover", such as collagen in connective tissue or the α-crystalline structures of the eye lens, which are exposed to glycation for practically the entire lifespan. The amounts of AGEs in body proteins increase with age.[142] In healthy adults, about 2 % of the body proteins have modified lysine or arginine residues, which is comparable to the degree of glycation of milk proteins after pasteurization.[143] The body proteins of diabetic patients are 2–3 times more strongly glycated than those of healthy adults (normoglycemics) because of the increased blood-sugar levels.[144] The main products of the glycation in vivo are the hydroimidazolones MG-H1 (**36**) and 3DG-H, as well as fructoselysine[143] and glucosepan (**35**).[101] That glucose emerged during the course of evolution to become the universal energy carrier in living systems may be due to the fact that, of the hexoses, it has the lowest percentage of open-chain form (carbonyl form) in solution and thus has the lowest reactivity in the Maillard reaction.[145]

4.2. Pathophysiology of Glycation In Vivo

Impairment of eyesight through clouding of the lens (cataract) is one of the most common consequences of diabetes. Cerami and Monnier showed that the spectroscopic changes to the eye lenses of diabetic patients can be induced if α-crystalline structures are incubated with reducing sugars or sugar phosphates.[146] Certain forms of cataract are even accompanied by a distinct yellow to brown coloration.[147] In the 1980s the adverse effects of the derivatization of lysine and arginine residues and protein cross-linking reactions during glycation on the functional properties of proteins and enzymes were considered to be the main causes for the long-term consequences of diabetes.[91] Various effects of diabetes correspond to typical "ageing diseases", which occur at a distinctly earlier age of patients with diabetes. In light of the newly identified role of the Maillard reaction in vivo and the respective carbohydrate-induced "ageing reactions" of proteins, attempts were also made to make glycation directly responsible for human ageing (glycation hypothesis of ageing[148]). Accordingly, the "phenotype" of ageing should be formed mainly from the accumulation and loss of function of glycated proteins. As attractive as this hypothesis of the "gradual saccharification" over the course of a lifetime may seem to be concrete molecular evidence for the cause of pathophysiological processes by the Maillard reaction in vivo predominantly originate from investigations in model systems up to now. Thus, for example, the loss of the catalytic activity of ribonuclease A during glycation could be directly attributed to the modification of two key lysine residues in the active center.[149] Methylglyoxal can modify arginine residues in integrin-interaction motifs of collagen and other proteins of the extracellular matrix to form MG-H1 (**36**) and thus "disguise" them, so that the resulting impaired cell–cell interaction can contribute to vascular dysfunction in diabetes patients.[150,151] Future investigations in model organisms could give more concrete indications about a correlation between glycation products and ageing processes. Thus, it was shown for *Caenorhabditis elegans* that the reduction in the lifespan of the nematode through high glucose concentrations in the medium coincides with an accumulation of AGEs on mitochondrial proteins, which are linked to raised oxidative stress.[152] A feeding of carbohydrate-modified proteins to *Drosophila melanogaster* likewise led to a shortening of the lifetime, which in this case is accompanied by a decrease in the protease activity in the proteasomes of the animals.[153]

Clear evidence for a causative role of glycation for long-term complications of diabetes has not yet been reported. New studies point to the overproduction of reactive oxygen species as the primary cause, which is due to an overload of the electron transport chain in mitochondrial membranes because of the increased glucose metabolism in insulin-insensitive cells. The consequence should be to "divert" glucose into other metabolic pathways and to enrich triose phosphates by the inhibition of glyceraldehyde-3-phosphate dehydrogenase, which is the central enzyme of glycolysis. 1,2-Dicarbonyl compounds can form from the triose phosphates[154] and then cause an intensified glycation.

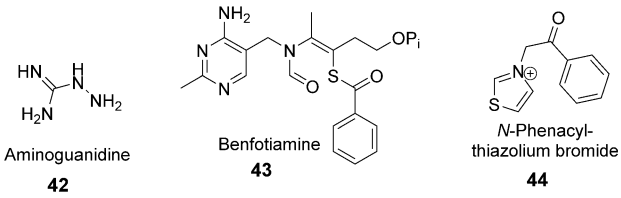
Vlassara et al. showed in 1985 that AGE-modified proteins can be bound to a special receptor (receptor for advanced glycation end products, RAGE).[155] The receptor was cloned and characterized for the first time in 1992.[156] Binding of ligands to the membrane-bound receptor triggers an intracellular signalling cascade in endothelial cells. This leads to the activation of the transcription factor NF-κB, which plays a key role in the molecular mechanisms of inflammation reactions.[157] For example, the endothelial surface is changed in such a way through NF-κB-dependant processes that coagulation events are favored.[158] AGE-modified proteins were initially discussed as ligands for RAGE. In particular, protein-bound carboxymethyllysine (**27a**) should be responsible for the binding of glycated proteins to the receptor,[159] whereby the in vivo circulating AGEs could participate in the long-term consequences of diabetes or uremia. It is, indeed, undisputed that RAGE is important in the etiology of vascular diseases.[160] However, new studies question if the activation of RAGE really results from AGE-modified proteins.[161]

Clear structure–response relationships regarding the significance of individual glycation products in defined pathophysiological processes in vivo have not yet been demonstrated successfully. The question of whether AGEs are the cause or the consequence (epiphenomena) of pathological processes, therefore, remains open. The toxicity of reactive dicarbonyl compounds is only concretely documented in uremia, and here especially during peritoneal dialysis.[162] 1,2-Dicarbonyl compounds, also denoted as "uremic toxins" in nephrology,[163] accumulate in the plasma in disorders of kidney function, but can also appear in large amounts during sterilization of glucose-rich peritoneal dialysis fluids.[164,165] For this reason, minimization strategies were developed, which resulted in the introduction of multichamber systems, in which glucose is sterilized separately from other ingredients.[166]

4.3. Pharmaceutical Intervention against Glycation

As a consequence of the postulated pathophysiological effects of glycation in vivo, attempts have been made since the 1980s to inhibit the Maillard reaction occurring in the body by using medication.[167] In the first very promising animal studies, the administration of large amounts of aminoguanidine (**42**; Scheme 8) could indeed prevent the late consequences of diabetes.[168] It was assumed that aminoguanidine traps the dicarbonyl compounds through the formation of triazines and thus can delay the formation of AGEs on proteins, but clinical studies on diabetic patients were disappointing: massive adverse effects resulted in the vision of a "drug against ageing" being abandoned for the time being.[169]

Pyridoxamine (vitamin B_6), thiamine (vitamin B_1), and benfotiamine (**43**) can also inhibit glycation reactions.[170,171] A further pharmacological strategy emerged with the discovery of "AGE breakers" such as *N*-phenacylthiazolium bromide (**44**), which is presumed to cleave the cross-linked structures in proteins.[172] However, the results of this pharmaceutical

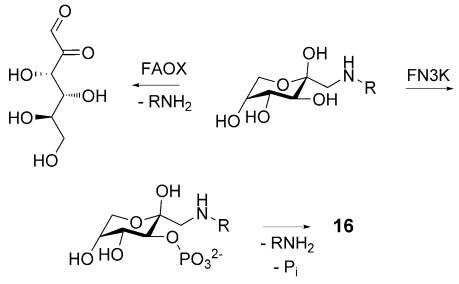


Scheme 8. Structures of AGE inhibitors and "AGE breakers". P_i = inorganic phosphate.

inhibition of AGE formation in vivo are also currently deemed to be not very convincing.[173] According to more recent investigations, the effects of most of the numerous AGE inhibitor and "AGE breaker" compounds can mainly be attributed to their chelating ability: they could simply inhibit autoxidation reactions which accompany glycation. A chelation therapy is accordingly being suggested for the symptomatic treatment of diabetes.[174]

4.4. Enzymatic Deglycation: Reversion of the Maillard Reaction In Vivo

Fructosylamine oxidases which catalyze the oxidative cleavage of Amadori products in several bacteria and fungi were first isolated and characterized in 1989.[175] In the 1990s, it was found that enzymatic deglycation reactions also take place in higher organisms. The research group of Szwergold reported for the first time that an enzyme in erythrocytes can convert fructose into fructose-3-phosphate with a very low affinity.[176] In 2000 and 2001, the search for a physiological substrate resulted in the isolation and cloning of two ketosamine kinases (fructosamine 3-kinase (FN3K) and fructosamine 3-kinase related protein (FN3K-RP)), which phosphorylate Amadori products with high affinity at the OH group in the C-3 position with consumption of ATP.[177–179] The unstable phosphate ester decomposes non-enzymatically, with regeneration of the amine (Scheme 9). Substrates of the ketosamine kinases are mainly protein-bound Amadori products, and thus modified lysine residues can return to their native state by this deglycation mechanism. Differences between the in vivo and in vitro glycation of hemoglobin[180] could now be explained by the different availabilities of individual ARP residues to FN3K.[181] The fact that "protective enzymes" for glycated body proteins have developed



Scheme 9. Enzymatic degradation of Amadori products.

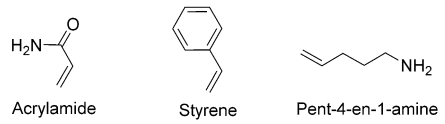
during the course of evolution, impressively emphasizes that the Maillard reaction in vivo is a "natural" and chemically unavoidable reaction, which always occurs when proteins are exposed to reducing carbohydrates.

5. Fourth Phase—Toxicological Relevance of Dietary Maillard Reaction Products

5.1. Process-Induced Food Toxicants

In 1959, Krug et al. showed in an animal study that the toxicity of amino acid/sugar mixtures can slightly increase upon heating,[182] but a toxicological relevance in nutrition, particularly in infants, was not inferred.[183] From the end of the 1970s, Maillard compounds which acted mutagenic in the Ames test were isolated from model preparations and foods, including heterocyclic aromatic amines (HAAs), HMF (**17**), and pyrraline (**28a**).[184] HAAs are formed during the Maillard reaction with the involvement of creatinine, and are thus found almost exclusively in roasted meats.[185] Certain heterocyclic amines are classified as potentially carcinogenic for humans. The data available on the content of the products in foods and on their bioavailability and metabolism are, however, not yet sufficient for a reliable risk evaluation.[186] A sulfation reaction in the hepatic phase II metabolism is held responsible for the mutagenicity of **17**.[187] The current perspective is that the amounts of HMF taken up in foods do not represent a risk to health.[188]

In 2001, occupational health examinations on the exposure of construction workers in Sweden to acrylamide ascertained that hemoglobin adducts of acrylamide (**45**) were also detectable in the blood of the non-exposed control group.[189] Shortly afterwards, the potentially carcinogenic acrylamide (**45**) was detected in relatively high amounts in foodstuffs for the first time, especially in strongly heated carbohydrate-rich products such as crispbread, crisps, and potato chips.[190] It was quickly clear that acrylamide originates from asparagine taking part in a Maillard reaction.[191,192] The formation occurs through a mechanism which was also observed for analogous compounds such as styrene (**46**; from phenylalanine) and pent-4-ene-1-amine (**47**; from lysine; Scheme 10).[193,194] For preventative healthcare reasons, considerable efforts to lower the acrylamide content in foods have been made (optimization of temperature/time processes during manufacture, use of potato and cereal variants low in asparagine, enzymatic degradation of asparagine).[195] Up to now, no clear correlation between the ingestion of acrylamide and an increased risk of cancer could be found in numerous epidemiological studies carried out.[196]



Acrylamide **45** | Styrene **46** | Pent-4-en-1-amine **47**

Scheme 10. Acrylamide and structurally analogous compounds in foods and model reactions.

5.2. AGEs as "Glycotoxins"

In 1997, Koschinsky et al. used an immunological method to show that dietary glycation products pass into the systemic circulation and that they are more or less quickly excreted depending on the kidney function. The authors concluded that compounds originating from food constitute a large part of the in vivo circulating AGEs.[197] Finally, the authors assumed that pathophysiological effects must, therefore, also emanate from dietary AGEs, which has led to the coinage of the very controversial term "glycotoxins".[197] The uptake of food rich in glycotoxins is presumed to provoke oxidative stress and inflammation reactions in the body. These hypotheses are, however, highly contentious. To date, measured physiological effects could not be unambiguously assigned to AGEs because of insufficient analytical characterization of the Maillard products present in the test meals[85,109] as well as possible other reactions occurring on heating of the food (vitamin degradation, lipid peroxidation).[198,199] In contrast, no detrimental effects of AGE-rich food were found in studies by other research groups.[200–202] On the basis of the current data, there is no perceptible advantage of restricting AGEs in the diets of diabetic patients.[203]

5.3. Metabolic Transit of Maillard Reaction Products

For both toxic and positive effects in the body, AGE-modified food proteins must be digestible and the resulting peptides and amino acids able to pass the intestinal epithelium. The first investigations in the 1940s were concerned with the digestibility of browned proteins, which can be restricted by modification of lysine and protein cross-linking.[122] At low levels of glycation, the release of amino acids—probably as a result of denaturing effects—can however be improved.[125]

Fructoselysine is almost completely released from heat-treated milk proteins by digestive enzymes into short-chain peptides,[204] but is not utilizable as a lysine source for rats.[205] If rats are fed with proteins glycated with radiolabeled glucose, a part of the radioactivity passes into the blood circulation. This indicates a bioavailability of other substances ("premelanoidins").[204] To date, only a few studies on the "metabolic transit" of dietary Maillard compounds using analytically fully defined substances can be found in the literature. The bioavailability of individual products is clearly crucially dependent on their structure. The largest part of the Maillard reaction products in foods, the Amadori products, are in effect not bioavailable for humans.[206–208] The bioavailability of HMF (**17**)[209] and CML (**27a**)[210] is low. In contrast, pyrraline (**28a**) (Scheme 3), which is taken up via food, appears in urine almost completely.[207] These differences in bioavailability are attributable to differences in the release and absorption properties: amino acid transporters are not able to transport glycated amino acids. Some glycated dipeptides, which can arise during luminal digestion, are however substrates for the intestinal peptide transporter PEPT1.[211] It had already been shown that nontransportable Amadori products can be degraded by the intestinal micro-

biota.[212] A specific mechanism of degradation by a two-stage enzyme system in *E. coli* was first described in 2002.[213]

6. Outlook: Maillard Reaction—Quo Vadis?

In terms of an overall mechanistic understanding of the course of the reaction, the formation and degradation of the Amadori products represent the most important focal point of the beginning of the Maillard reaction.[6] The identification of such focal points in later stages of the reaction could result in a deeper understanding of the formation of melanoidins. Similar to the structural characterization of humic acids,[214] aspects of supramolecular chemistry can be of significance here. It is expected that an abundance of hitherto unknown glycation products will be isolated from model reaction systems and identified and quantified in foods and the human body.

It remains crucial for future physiological and chemical research to explain the open question of whether the measurable glycation products in vivo are really the cause of defined pathophysiological processes or if they simply evolve as an epiphenomenon. Here, we consider it essential that chemically exact and analytically clear terminology is used to describe the Maillard reaction products, particularly in biomedicine-orientated research and literature. The term "AGE" describes, as detailed in this Review, a virtually unmanageable variety of individual compounds. Correspondingly, information on the "AGE content" and studies on "effects induced by AGEs" without firmly establishing the fundamental chemistry to deduce structure–property relationships is ultimately not very meaningful. To clearly demonstrate the relevance of the Maillard reaction for certain medical conditions, physiological effects must be attributed to chemically and analytically distinct, rational structures in in vivo studies. Metabolites of Maillard reaction products, which for example are formed in the liver and kidneys or by the intestinal microbiota, must also be examined. Similarly to acrylamide (**45**), the potential toxicity of dietary glycation products must be evaluated in this context. A sound risk assessment of individual compounds is thus an interdisciplinary challenge for preparative and analytical chemistry, biology, and medicine.[215]

From a food chemistry viewpoint, the bulk of the latest literature on the Maillard reaction deals with glycation products as process contaminants, that is, as "undesired", because of potentially toxic or antinutritive compounds. Less attention has often been paid to publications, especially in the last few years, which discuss interesting positive aspects of Maillard reaction products.[216] For example, in many studies it was shown that melanoidins function in vitro and in vivo as antioxidants, and as prebiotics they can positively influence the composition of the intestinal microbiota.[217,218] An increased antioxidative capacity in the plasma of rats was observed after feeding them bread crusts or malt with a defined content of pronyllysine (**33** in Scheme 6). This was caused by the activation of potential "chemopreventative" enzyme systems such as glutathione-S-transferase (GST) and UDP glucuronyl transferase (UDP-GT).[219] Furanones, pyranones, and cyclopentenones isolated from model reactions and identified as chromophoric precursors for the formation of melanoidins functioned as inhibitors of the growth of tumor cells in vitro in micromolar concentrations, possibly through inhibition of the phosphorylation of the transcription factor Elk-1.[220,221] Coffee melanodins in physiologically relevant concentrations are efficient inhibitors of certain matrix metalloproteinases, to which a central role in the pathogenicity of colorectal cancers is accredited.[222]

Current literature reports indicate that hominids were already able to control fire about one million years ago[223] and this ability presumably also applied to heating foods—and thus ultimately they used the Maillard reaction. The improvement in the preservation, digestibility, odor, and taste by heating foods is beyond dispute. According to a current theory of anthropological research, the use of fire in food preparation was a decisive evolutionary advantage in human development.[126] If one assumes that the food of humans has contained a considerable proportion of Maillard products due to its preparation for several hundred thousand years, then questions almost inevitably arise about a possible relevance in the evolutionary biology of these food components. Did the metabolism of *Homo sapiens* adapt to a biological use of glycation products? Do we have "species-specific" detoxification systems, for example, for highly reactive dicarbonyl compounds (see Scheme 3)? Are dietary amino acid derivatives of the Maillard reaction important in combination or in competition with the "conventional" amino acids for signal transduction pathways? Did the microbiota of the colon adapt to utilize the Maillard products which are not resorbed in the small intestine, and thus are the corresponding compounds significant as prebiotic structures for the integrity of the human intestinal flora?

Regarding the fundamental importance of his observations, Maillard was himself surprised, "*that it (the reaction) is not yet known in its smallest details.*"[1] We are convinced that the Maillard reaction still holds many surprises, even after over one hundred years of research.

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