Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Chromatography B, 802 (2004) 3–10
JOURNAL OF CHROMATOGRAPHY B
www.elsevier.com/locate/chromb

Formation of heterocyclic aromatic amines in model systems

M. Murkovic*

Department of Food Chemistry and Technology, Graz University of Technology, Petersgasse 12/2, 8010 Graz, Austria

Abstract

Heterocyclic aromatic amines (HAs) are mutagenic and carcinogenic substances that are formed in significant amounts during heating of meat or fish at temperatures of at least 150 °C. To investigate the chemistry lying behind the formation of these harmful substances model systems were established. The first aim was to identify the naturally occurring precursors, namely creatinine, amino acids and carbohydrates. Later these model systems were used to develop strategies for a reduction of the content of the heterocyclic aromatic amines and for the evaluation of the reaction mechanisms that lead to the formation of these substances. All these aspects are discussed in this review.

Keywords: Model systems; Heterocyclic aromatic amines

1. Introduction

Heterocyclic aromatic amines (HAs) are substances with a high mutagenic and carcinogenic potential [1]. They occur in heated meat and fish. During boiling of meat the HAs are formed at very low concentrations but if the cooking temperature is increased above 150 °C the formation of the HAs increases significantly. These temperatures are reached at the surface when meat or fish is fried, grilled, baked, or roasted. Research on carcinogenicity of heated meat goes back to the year 1939 when the Swedish chemist Widmark found that extracts of fried horse meat induces cancer if they are applied to the skin of mice [2]. Further research on mutagenicity and carcinogenicity was reviewed by Sugimura [3]. The HAs identified and characterized to date are summarized in Table 1. The chemical names that are commonly used are not according to the latest IUPAC rules but give an explanation for the internationally used abbreviations.

In general, the HAs can be divided into two groups namely the polar which are mainly of the imidazoquinoline type (IQ) and imidazoquinoxaline type (IQx) as well as the imidazopyridine type (Figs. 1 and 2) and the non-polar which have a common pyridoindole or dipyridoimidazole moiety (Fig. 3).

The polar HAs are formed from amino acids, carbohydrates and creatinine. Especially creatinine is necessary since from it the imidazo moiety is formed. If it is not present no HAs of the IQ and IQx type are formed. The temperature that is needed for the formation of significant amounts is between 150 and 250 °C. At higher temperatures the non-polar HAs are formed preferably. They are usually assigned as pyrolysis products of the amino acids.

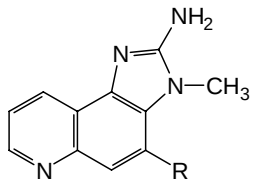
The concentration of the HAs is normally in the low ppb range. Using the Ames test the mutagenicity can be tested using sensitive bacterial test strains. The carcinogenicity was shown in mouse and rat models [3]. The International Agency for Research on Cancer [4] collated the studies on carcinogenicity and classified IQ as *probably carcinogenic to humans* (*Group 2A*) and MeIQ as well as MeIQx and PhIP and the apolar HAs AαC, MeAαC, Glu-P-1, Glu-P-2, Trp-P-1, and Trp-P-2 as *possibly carcinogenic to humans* (*Group 2B*). Further work on the carcinogenicity of HCA has underlined the mutagenic and carcinogenic potential of these substances.

The formation of the HAs can be studied in chemical model systems [5]. The advantage of the model system is that complex side reactions are reduced and reactions from other constituents of the meat that are not involved in the formation of the HAs are excluded. Additionally, some of the HAs were first identified in the model systems and later found in heated meat.

This review will give a critical overview of the investigative work on formation of these carcinogenic compounds by using model systems.

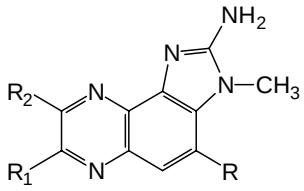
* Tel.: +43-316-8736495; fax: +43-316-8736971.
E-mail address: michael.murkovic@tugraz.at (M. Murkovic).

1570-0232/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.jchromb.2003.09.026



IQ: R = H

MeIQ: R = CH_3



IQx: R = H, R_1 = H, R_2 = H

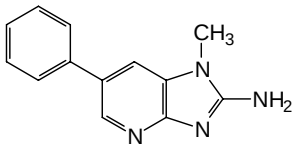
MeIQx: R = H, R_1 = H, R_2 = CH_3

4,8-DiMeIQx: R = CH_3, R_1 = H, R_2 = CH_3

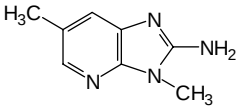
7,8-DiMeIQx: R = H, R_1 = CH_3, R_2 = CH_3

4,7,8-DiMeIQx: R = CH_3, R_1 = CH_3, R_2 = CH_3

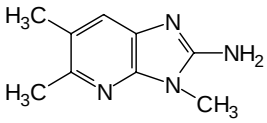
Fig. 1. Structures of IQ and IQx type HAs.



PhIP

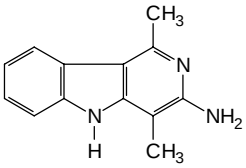


DMIP

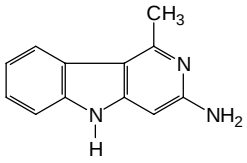


TMIP

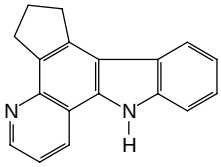
Fig. 2. Other polar HAs.



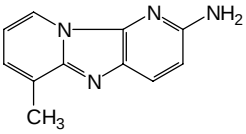
Trp-P-1



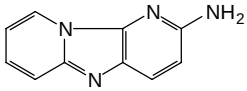
Trp-P-2



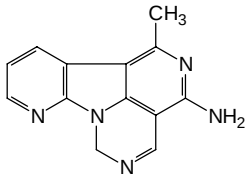
Lys-P-1



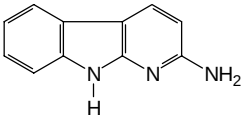
Glu-P-1



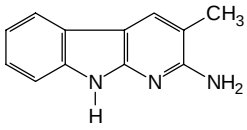
Glu-P-2



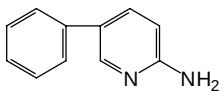
Orn-P-1



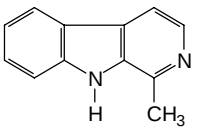
AαC



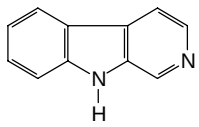
MeAαC



Phe-P-1



Harman



Norharman

Fig. 3. Selection of non-polar HAs.

Table 1
Heterocyclic aromatic amines

Quinolines	
IQ	2-Amino-3-methylimidazo[4,5-*f*]quinoline
MeIQ	2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline
Quinoxalines	
IQx	2-Amino-3-methylimidazo[4,5-*f*]quinoxaline
MeIQx	2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline
4,8-DiMeIQx	2-Amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline
7,8-DiMeIQx	2-Amino-3,7,8-trimethylimidazo[4,5-*f*]quinoxaline
4,7,8-TriMeIQx	2-Amino-3,4,7,8-tetramethylimidazo[4,5-*f*]quinoxaline
4-CH_2OH-8-MeIQx	2-Amino-4-hydroxymethyl-3,8-dimethylimidazo[4,5-*f*]quinoxaline
7,9-DiMeI*g*Qx	2-Amino-1,7,9-trimethylimidazo[4,5-*g*]quinoxaline
Pyridines	
PhIP	2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine
4′-OH-PhIP	2-Amino-1-methyl-6-(4-hydroxyphenyl)imidazo[4,5-*b*]pyridine
DMIP	2-Amin-1, 6-dimethylimidazo[4,5-*b*]pyridine
TMIP	2-Amino-1,5,6-trimethylimidazo[4,5-*b*]pyridine
Furopyridines	
IFP	2-Amino-1,6-dimethylfuro[3,2-*e*]imidazo[4,5-*b*]pyridine
Pyridoimidazoles and indoles	
Trp-P-1	3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole
Trp-P-2	3-Amino-1-methyl-5*H*-pyrido[4,3-*b*]indole
Glu-P-1	2-Amino-6-methyl-dipyrido[1,2-*a*:3′,2′-*d*]imidazole
Glu-P-2	2-Amino-dipyrido[1,2-*a*:3′,2′-*d*]imidazole
AαC	2-Amino-9*H*-pyrido[2,3-*b*]indole
MeAαC	2-Amino-3-methyl-9*H*-pyrido[2,3-*b*]indole
Norharman	β-Carboline
Harman	9-Methyl-β-carboline
Benzoxazines	
	2-Amino-3-methylimidazo[4,5-*f*]-4*H*-1,4-benzoxazine
	2-Amino-3,4-dimethylimidazo[4,5-*f*]-4*H*-1,4-benzoxazine
Other structures	
Lys-P-1	3,4-Cyclopentenopyrido[3,2-*a*]carbazole
Orn-P-1	4-Amino-6-methyl-1*H*-2,5,10,10*b*-tetraaza-fluoranthene
Phe-P-1	2-Amino-5-phenylpyridine

2. Identification of the precursors

The first published model systems where mutagenic compounds were identified were pyrolysis reactions of amino acids and proteins. Other food constituents did not form mutagenic substances during pyrolysis [6,7]. The substances identified were the same as found in the charred parts of roasted or grilled meat and fish [8]. Nucleic acids, starch, or oil did not form mutagenic substances during pyrolysis. Heating of single amino acids also resulted in the formation of mutagenic substances that were identified as heterocyclic aromatic amines. In general, the products of pyrolysis assigned as non-polar HAs are listed in Fig. 3. In contrast, harman and norharman are both formed at lower temperatures and Trp-P-1 was also shown to occur in cooked meat which was prepared at lower temperatures [9]. In contrast to the non-polar HAs the polar HAs are formed at normal cooking temperatures. These mutagens were identified in fried meat and fish. They were also found in meat products, e.g. in meat extract that is extracted at comparably low temperatures but using longer times for processing.

Most polar HAs are formed from creatine or creatinine, amino acids and carbohydrates. The heating of the reaction systems was done as a dry powder or dissolved in diethylene glycol. Both methods of heating lead to the same heterocyclic aromatic amines with more or less the same quantitative results. All this work is reviewed in [10].

When using meat juice for model systems the complexity increases since several polar and non-polar HAs are formed [9,11]. Since the composition of the precursors (amino acids, glucose, creatine) simulates the chemical environment in the meat much better than a solution of single amino acids in diethylene glycol the results are more relevant but much more complicated to interpret. Depending on the type of meat from which the juice is derived the amino acid composition and the glucose and creatine content vary to a great extend. This results in a specific pattern of the formed HAs.

3. Chemistry of HCA formation

At the beginning of last century, Maillard proposed the browning reaction to account for the brown pigments and polymers produced from the reaction of the amino group of an amino acid and the carbonyl group of a sugar [12]. The chemistry underlying the Maillard reaction is very complex. It encompasses not one reaction pathway but a whole network of various reactions. The original comprehensive reactions scheme of Hodge [13] has been improved continuously since that time. At some stages of the browning reaction, e.g. pyrazines [14] quinoxalines [15] and pyrido[3,4-*d*]imidazoles [16] are formed that are involved in the formation of HAs. The formation of mutagens during the Maillard reaction was shown by the groups of Spingarn and Garvie [17], Shibamoto et al. [18], and Wei et al. [19].

The involvement of the *N*-heterocycles derived from the Maillard reaction in the formation of HAs is shown in Fig. 4. It can be seen that methylated pyridines and pyrazines are precursors in this reaction pathway. Aldehydes that are also products resulting from the high temperature reaction are necessary as well as creatinine which forms the imidazo moiety of all polar HAs [20].

Experiments using ^{14}C-labelled glucose in a model system with threonine and creatinine showed that the radioactive C-atoms of the glucose are incorporated into the HAs [21]. A combination of these results with those of Hwang et al. [14] lead to the suggestion that the carbon atoms from the pyridine or pyrazine moiety originate from glucose which is cleaved into two C-3-fragments. Additionally, the C-4 of the HAs is derived from the C-2 of the amino acid (Fig. 5).

3.1. Stability of HAs during heating

A study by Chiu and Chen [22] showed that the HAs are degraded depending on temperature and time. The degradation followed first order kinetics in the temperature range between 100 and 200 °C. The activation energy for the degradation was in the range of 1.9 kJ/mol for MeIQx and 19.7 kJ/mol for Norharman. Earlier work from Arvidsson et al. [23] gave similar results. In both studies PhIP was the most susceptible to degradation at 225 °C followed by the quinoxalines.

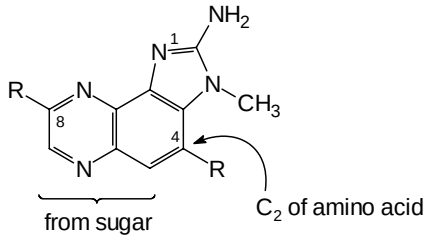


Fig. 5. Origin of carbon atom of IQ and IQx type HAS ([21]).

3.2. Influence of polyphenols on the formation of HAs

Lee et al. [24] investigated the formation of MeIQx and 7,8-DiMeIQx in a model system containing glycine, creatinine and glucose. The mixture was heated in the azeotrop of diethylene glycol with 14% water at a boiling temperature of 128 °C. The addition of flavone led to a significant reduction of the mutagenicity of the fractions eluting at the same time from a chromatographic column as MeIQx and 7,8-DiMeIQx. They suggested that flavone inhibits the formation of Maillard reaction products which are necessary for the formation of the HAs.

Fukuhara et al. [25] found that the mutagenic activity and the contents of 2-amino-9*H*-pyrido[2,3-*b*]indole in pyrolysates of albumin were decreased by the addition of tannic acid, quercetin, rutin, catechin, *n*-propylgallate and BHA. The same model system was used by other authors [26] but phenols from olive oil were investigated. Fresh olive oil inhibited the formation of IQx, MeIQx, and 4,8-DiMeIQx by 45–60%, whereas 1-year-old oil inhibited the HCA formation to a much lower extend. Isolated phenolic compounds from olive oil also inhibited the formation of the mentioned HAs.

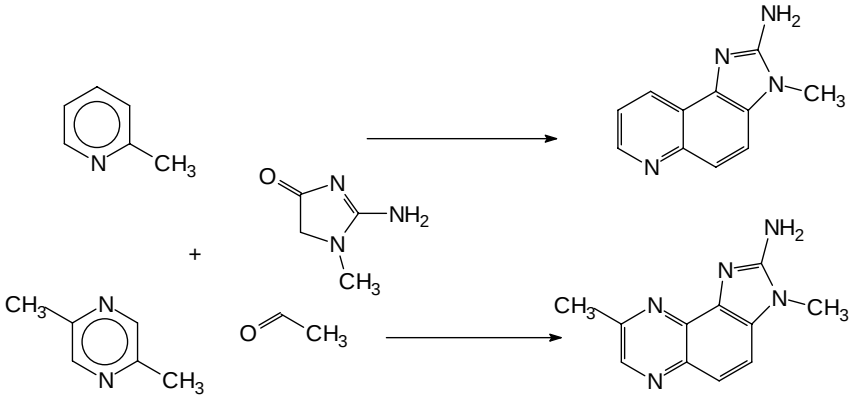


Fig. 4. Formation of imidazoquinolines and imidazoquinoxalines from products of the Maillard reaction (2-methyl-pyridine, 2,5-dimethyl-pyrazine) with acetaldehyde and creatinine [29].

3.3. Involvement of radicals

Two different pathways for free radical formation are proposed. One involves bimolecular ring formation from the enaminol form of the glycoaldehyde alkylimine which is followed by oxidative formation of the free radical. The other pathway involves formation of *N*,*N*1-dialkylpyrazinium ions from glyoxal monoalkylimine followed by a reduction to produce the free radicals. The respective intermediates (glycoaldehyde alkylimine and glyoxal monoalkylamine) are formed by reacting glycoaldehyde and glyoxal with amino compounds. The glycoaldehyde system reacts faster and produces more free radicals than the glyoxal system. The reaction helps to explain the formation of IQx meat mutagens and their predominance in fried fish and beef and why these mutagens are present in larger quantities in fried ground beef than the IQ-type mutagens [27] (Fig. 6).

The mechanisms of the mutagen formation involving the free radical Maillard intermediates, pyrazine (or pyridine) cation radicals, have been offered [27]. There are a few lines of evidence for supporting the free radical mechanisms in the mutagen formation. Imidazoquinoxaline-type mutagens are formed in the model mixture composed of glucose, glycine and creatinine through the free radical Maillard intermediates, a pyrazine cation radical and carbon-centred radicals [28–31]. In the initial stage of the Maillard reaction of glucose with glycine, both the pyrazine cation radical and the carbon-centred radicals are generated, and they are scavenged in the presence of phenolic antioxidants [28]. Kikugawa et al. have shown [32] that in this model system the pyrazine cation radical is dominantly formed. Formation of imidazoquinoxaline-type mutagens in the model mixture composed of glucose, glycine, and creatinine is reduced in the presence of phenolic antioxidants including epigallocatechin gallate [28]. Epigallocatechin gallate and flavonoids similarly prevent the mutagens in the model mixture of glucose, glycine and creatinine [33].

It has been shown that heating a mixture of glucose with glycine in diethylene glycol as solvent at 120 °C for 5 min gives characteristic multi-line ESR signals due to the 1,4-di(carboxymethyl)pyrazine cation radical [28]. Generation of the carbon-centred radicals in the mixture heated for 5 min is also observable by ESR-spin trapping technique using 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and *N*-*tert*-butyl-α-phenylnitrone (PBN) [28].

3.4. Formation of norharman

A defined mechanism was described for the formation of Norharman a non-polar HCA [34]. Norharman itself is not mutagenic but in presence of aniline it becomes a comutagen [35]. According to the mechanism shown in Fig. 7, the tryptophan Amadori rearrangement product (ARP) (1) in the furanose form undergoes a dehydration reaction followed by

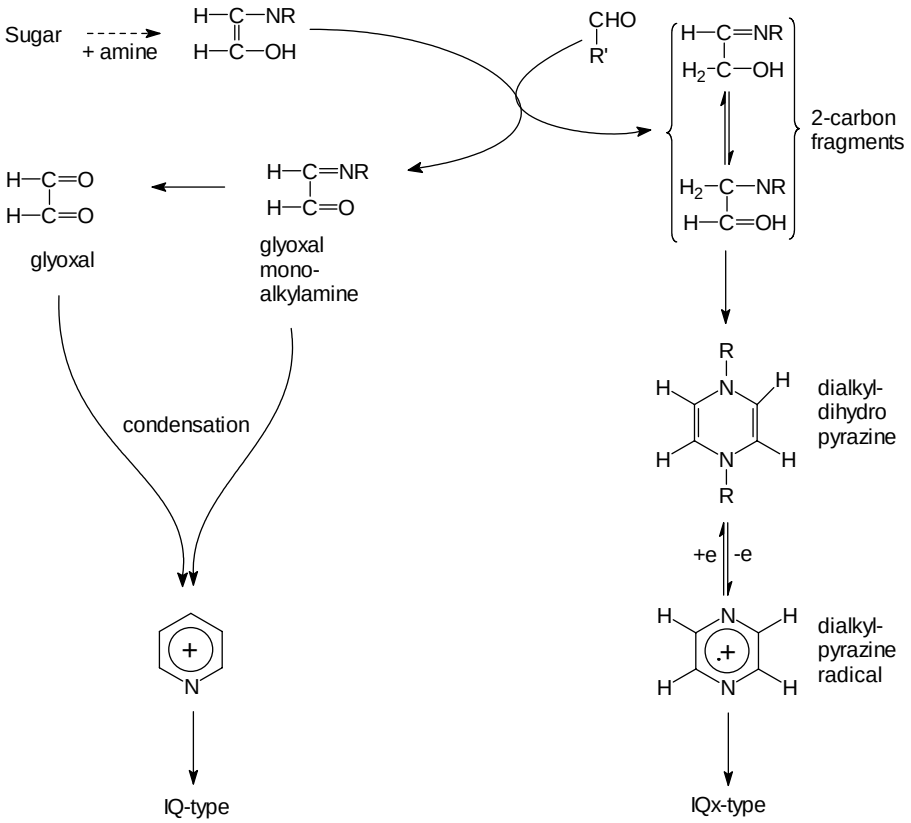


Fig. 6. Suggested pathway for formation of IQ-type and IQx-type compounds (adopted from [27]).

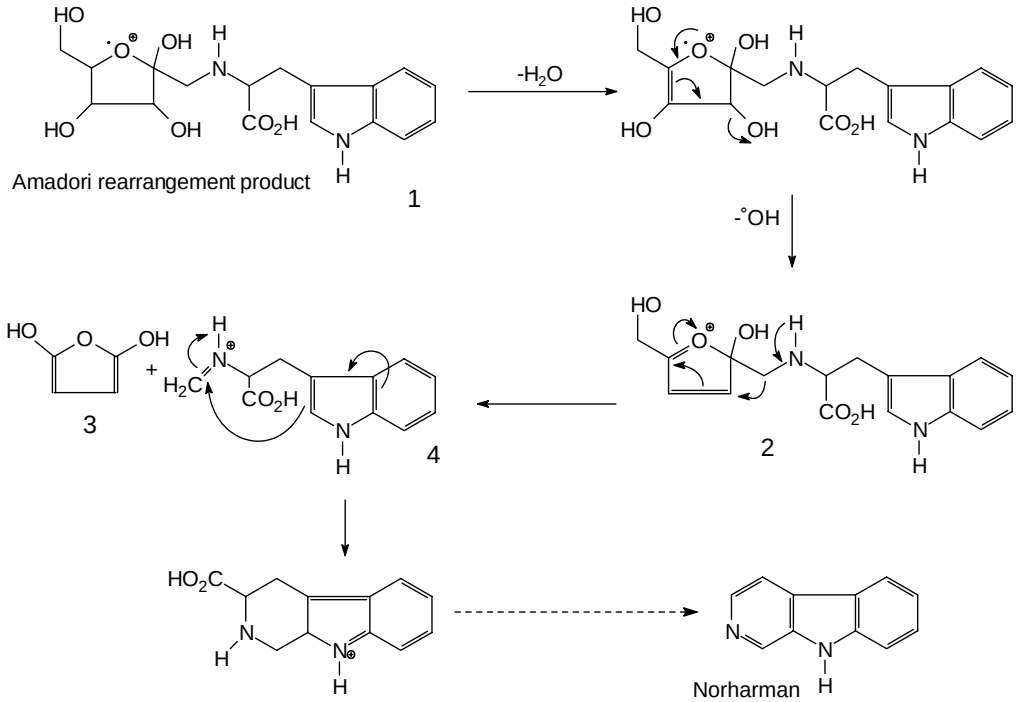


Fig. 7. Formation of Norharman from tryptophan Amadori rearrangement product (adopted from [34]).

β-elimination assisted by the lone pair electrons of the ring oxygen forming a conjugated oxonium ion. This reactive intermediate can either stabilize itself further by dehydration and formation of an extended conjugated system, or it can undergo a C–C bond cleavage to produce a neutral furan derivative (3) and an imminium cation (4). Subsequently, the intermediates can undergo intramolecular nucleophilic substitution reactions to form β-carbolines.

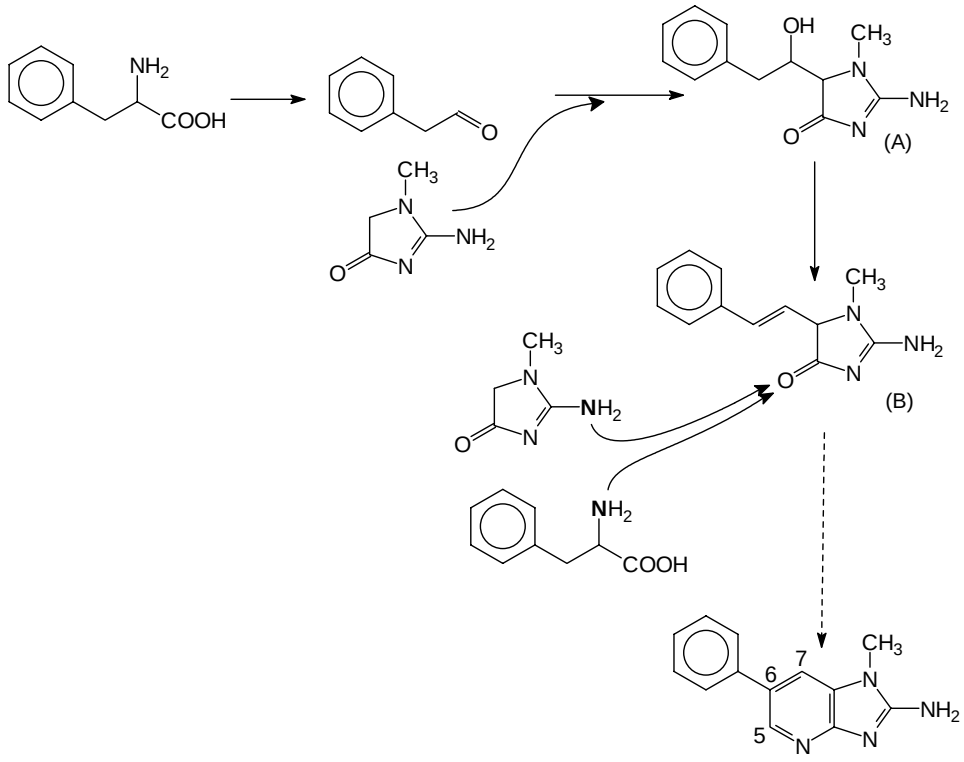


Fig. 8. Formation of PhIP with identified intermediate reaction products (adopted from [42,43]).

3.5. Formation of PhIP

Using model systems Shioya et al. [36] showed that phenylalanine, creatinine and glucose were probable precursors of PhIP. By dry heating of ^{13}C-labelled phenylalanine and creatinine it has been convincingly demonstrated that phenylalanine and creatinine are precursors of PhIP [37]. PhIP may also be produced from creatine heated together with leucine, isoleucine and tyrosine. Accordingly, glucose seems not to be a necessary precursor using dry heating conditions [38]. However, glucose was found to have a considerable influence, either enhancing or inhibiting depending on its concentration, on the yield of PhIP produced from phenylalanine and creatine in a liquid model system [39] and also during dry heating [37]. Manabe et al. [40] reported that a tetrose (erythrose) is the most active in the formation of PhIP, when phenylalanine and creatinine dissolved in water is heated at temperatures of 37 and 60 °C. The other carbohydrates namely arabinose, ribose, glucose and galactose are not as active. This group found PhIP in heated mixtures of creatinine, phenylalanine and aldehydes [40], as well as in mixtures of phenylalanine, creatinine and nucleic acids [41]. The 4′-hydroxy derivative of PhIP was found in an analogous reaction using tyrosine instead of phenylalanine [42].

The formation of PhIP in the simple model system with just phenylalanine and creatinine as precursors starts with the formation of the Strecker aldehyde phenylacetaldehyde. The second step is an aldol condensation of the aldehyde with creatinine and subsequently the dehydration. Both products the addition [A] as well as the condensation [B] product were identified in the model system and in heated meat as well [43]. The origin of the nitrogen forming the pyridine moiety of PhIP is at least twofold. First it can be the amino group of creatinine which reacts with the oxo group of the intermediate and second the amino group of phenylalanine or even free ammonia. The origin of the carbon atoms 5, 6 and 7 in PhIP was identified by the use of ^{13}C-labelled phenylalanine (labelled at C-2 and C-3, respectively) and analysing the formed PhIP by NMR [44]. Combining these results a mechanism for the formation of PhIP was formulated (Fig. 8).

4. Conclusion

Thus far, several efforts to minimize the mutagen formation in the Maillard-type reaction have been done. The best way to minimize the mutagen formation is by blocking the non-radical pathway of the mutagen formation. Addition of amino acid derivatives reduces the mutagen formation. Jones and Weisburger have demonstrated that tryptophane [45], indole derivatives [46] and proline [47] added to the model system or to beef reduces the mutagen formation by masking the reactive aldehydes. Sugar is also an important factor to reduce the mutagenicity. Skog and Jägerstad have shown that an excessive amount of sugars in the model system [39,48] reduces the mutagen formation by masking creatinine. This inhibitory effect was not only observed in the model system but also when meat was heated in presence of excessive concentrations of carbohydrates [49]. Therefore, the sugar content may be important for minimizing mutagen formation due to the Maillard reaction.

References

[1] T. Sugimura, Mutat. Res. 376 (1997) 211.
[2] E. Widmark, Nature 143 (1939) 984.
[3] T. Sugimura, in: R.H. Adamson, A.A. Gustafsson, N. Ito, M. Nagao, T. Sugimura, K. Wakabyashi, Y. Yamazoe (Eds.), Proceedings of the 23rd International Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, 1995, Princeton Scientific, 1995, p. 214.
[4] International Agency for Cancer Research 56 (1993) 163.
[5] M. Jägerstad, K. Skog, P. Arvidsson, A. Solyakov, Z. Lebensm. Unters. Forsch. A 207 (1998) 419.
[6] M. Nagao, M. Honda, Y. Seino, T. Yahagi, T. Sugimura, Cancer Lett. 2 (1977) 335.
[7] T. Sugimura, M. Nagao, T. Kawachi, M. Honda, T. Yahagi, Y. Seino, S. Sato, M. Matsukura, T. Matsushima, A. Shirai, M. Sawamura, M. Matsumoto, in: H.H. Hiatt, J.D. Watson, J.A. Winsten (Eds.), Origin of Human Cancer, Cold Spring Harbour Laboratory, Cold Spring Harbour, New York, 1977, p. 1561.
[8] M. Nagao, M. Honda, Y. Seino, T. Yahagi, T. Sugimura, Cancer Lett. 2 (1977) 221.
[9] P. Arvidsson, M.A.J.S. vanBoekel, K. Skog, M. Jägerstad, J. Food Sci. 64 (1999) 216.
[10] M. Jägerstad, K. Skog, S. Grivas, R. Olsson, Mutat. Res. 259 (1991) 219.
[11] E. Borgen, A. Solykov, K. Skog, Food Chem. 74 (2001) 11.
[12] L. Maillard, Compt. Rend. 154 (1912) 66–68.
[13] J.E. Hodge, J. Agric. Food Chem. 1 (1953) 928.
[14] H.-I. Hwang, T.G. Hartman, R.T. Rosen, J. Lech, C.-T. Ho, J. Agric. Food Chem. 42 (1994) 1000.
[15] N. Morita, M. Takagi, in: P.A. Finot, H.U. Aeschbacher, R.F. Hurrell, R. Liardon (Eds.), The Maillard Reaction in Food Processing, Human Nutrition and Physiology, Birkhäuser, Basel, 1990, p. 59.
[16] U.S. Gi, W. Baltes, in: T.P. Labuza (Ed.), Maillard Reactions in Chemistry, Food and Health, Royal Society of Chemistry, Cambridge, 1994, p. 106.
[17] N. Spingarn, C. Garvie, J. Agric. Food Chem. 27 (1979) 1319.
[18] T. Shibamoto, D. Nishimura, S. Mihara, J. Agric. Food Chem. 29 (1981) 643.
[19] C.I. Wei, K. Kitamura, T. Shibamoto, Food Chem. Toxicol. 19 (1981) 749.
[20] M. Jägerstad, A. Laser Reutersward, R. Olsson, S. Grivas, T. Nyhammar, K. Olsson, A. Dahlqvist, Food Chem. 12 (1983) 255.
[21] K. Skog, M. Jagerstad, Carcinogenesis 14 (1993) 2027.
[22] C.P. Chiu, B.H. Chen, Food Chem. 68 (2000) 267.
[23] P. Arvidsson, M.A.J.S. vanBoekel, K. Skog, M. Jägerstad, J. Food Sci. 62 (1997) 911.
[24] H. Lee, C.Y. Jiaan, S.J. Tsai, Food Chem. 45 (1992) 235.
[25] Y. Fukuhara, D. Yoshida, G. Goto, J. Agric. Biol. Chem. 45 (1981) 1061.
[26] S.M. Monti, A. Ritieni, R. Sacchi, K. Skog, E. Borgen, V. Fogliano, J. Agric. Food Chem. 49 (2001) 3969.
[27] A.M. Pearson, C. Chen, J.I. Gray, S.D. Aust, Free Radic. Biol. Med. 13 (1992) 161.
[28] T. Kato, T. Harashima, N. Moriya, K. Kikugawa, K. Hiramoto, Carcinogenesis 17 (1996) 2469.
[29] B.L. Milic, S.M. Djilas, M.C.B. Jasna, Food Chem. 46 (1993) 273.

[30] M. Johansson, M. Jägerstad, Food Chem. 56 (1996) 69.
[31] K. Skog, M.A. Johansson, M. Jagerstad, Food Chem. Toxicol. 36 (1998) 879.
[32] K. Kikugawa, T. Kato, K. Hiramoto, C. Takeda, M. Tanaka, Y. Maeda, T. Ishihara, Mutat. Res. 444 (1999) 133.
[33] A. Oguri, M. Suda, Y. Totsuka, T. Sugimura, K. Wakabayashi, Mutat. Res. 402 (1998) 237.
[34] V. Yaylayan, J.R. Jocelyn Paré, R. Laing, P. Sporns, in: P.A. Finot, H.U. Aeschbacher, R.F. Hurrell, R. Liardon (Eds.), The Maillard Reaction in Food Processing, Human Nutrition and Physiology, Birkhäuser, Basel, 1990, p. 115.
[35] K. Wakabayashi, Y. Totsuka, K. Fukutome, A. Oguri, H. Ushiyama, T. Sugimura, Mutat. Res. 376 (1997) 253.
[36] M. Shioya, K. Wakabayashi, S. Sato, M. Nagao, T. Suigmura, Mutat. Res. 191 (1998) 133.
[37] J.S. Felton, M.G. Knize, in: H. Hayatsu (Ed.), Mutagens in Food, Detection and Prevention, CRC Press, Boca Raton, 1991, p. 57.
[38] K. Skog, M.A.E. Johansson, M. Jägerstad, Food Chem. Toxicol. 36 (1998) 879.
[39] K. Skog, M. Jägerstad, Mutat. Res. 230 (1990) 263.
[40] S. Manabe, N. Kurihara, O. Wada, K. Tokyama, T. Aramaki, Carcinogenesis 13 (1992) 827.
[41] S. Manabe, K. Suzuki, O. Wada, A. Veki, Carcinogenesis 14 (1993) 899.
[42] K. Wakabayashi, T.S. Kim, R. Kurosaka, Z. Yamaizumi, H. Ushiyama, M. Takahashi, S. Koyota, A. Fecuda, H. Nukaya, S. Goto, T. Sugimura, M. Nagao, in: P.H. Adamson, J.A. Gustavsson, N. Ito, M. Nagao, T. Sugimura, K. Wakabayashi, Y. Yamazoe (Eds.), Heterocyclic Amines in Cooked Foods: Possible Human Carcinogens, Princeton Scientific Publishing, Princeton, 1995, p. 197.
[43] S. Zöchling, M. Murkovic, Food Chem. 79 (2002) 125.
[44] M. Murkovic, H.J. Weber, S. Geiszler, K. Fröhlich, W. Pfannhauser, Food Chem. 65 (1999) 233.
[45] R.C. Jones, J.H. Weisburger, Mutat. Res. 206 (1988) 343.
[46] R.C. Jones, J.H. Weisburger, Jpn. J. Cancer Res. 79 (1988) 222.
[47] R.C. Jones, J.H. Weisburger, Environ. Mol. Mutagen. 11 (1988) 509.
[48] K. Skog, M. Jägerstad, Carcinogenesis 12 (1991) 2297.
[49] K. Skog, M. Jagerstad, A.L. Reutersward, Food. Chem. Toxicol. 30 (1992) 681.