Structure-Activity Relationships of Natural Volatile Nitrogen Compounds

By Mans H. Boelens, Boelens Aroma Chemical Information Service, and Leo J. van Gemert, TNO Nutrition and Food Research Institute, The Netherlands

Volatile nitrogen compounds are often important for the sensory properties of food flavors and natural isolates. Character-impact nitrogen compounds have been found, for instance, in the flavors of processed foods and drinks, such as bread, meat, coffee and cocoa. During the last decade, much attention has been paid to the identification and sensory properties of nitrogen compounds from natural isolates, such as headspaces and absolutes of flowers and essential oils.

Last year in the September/October issue of this magazine we studied the occurrence, identities and sensory properties of volatile nitrogen compounds emitted by flowers and isolated from flower absolutes and essential oils. Now we have investigated the threshold values and structure-activity relationships of natural volatile aliphatic and aromatic nitrogen compounds, substituted pyridines, quinolines, pyrazines and thiazoles.

Introduction

It is general knowledge that volatile nitrogen compounds are, from a sensory point of view, important constituents of flavors. Thorough reviews about this subject have been published.[1-7] Researchers in the early 1970s tried to determine the sensory properties (i.e., odor and flavor qualities and threshold values in different media) of these flavor compounds. During the last decade, the identification and determination of the sensory properties of volatile nitrogen compounds from natural isolates have come more and more into focus. Interest arose from improvements in isolation and concentration of volatile trace constituents of natural products, and from modern chromatographic techniques. These techniques include, for instance, gas chromatography on high-resolution, high-precision fused silica capillary columns. An excellent review on headspace analysis by modern gas chromatographic methods was written by Bicchi.[8]

Formerly, say about 25 years ago, little attention was paid to trace constituents present in concentrations below 0.01% (100 ppm) in an essential oil. Nowadays it is possible to quantify compounds in concentrations less than 1 part per billion (0.001 ppm). In this paper, we will discuss the sensory properties of various representatives of volatile nitrogen compounds and their structure-activity relationships.

Sensory Properties of Nitrogen Compounds

The determination of the sensory properties of nitrogen compounds is a complicated matter, as it is for other chemical compounds. First, this determination is rather subjective, due to intra- and interindividual differences. Each human being has numerous receptor sites,[135] which may vary in sensitivity from site to site and from one person to another.

Second, the qualitative sensory properties of the compounds often are strongly dependent on their concentration. This olfactive dependence on stimulant concentration may be caused by the so-called "multiplicity of the compound." Multiplicity of a compound is a compound's ability to trigger different receptor sites at various concentrations. Another aspect of the sensory evaluation of nitrogen compounds is that the determination of the odor quality often is influenced by the degree of pleasantness or unpleasantness. Buttery et al.,[9] for instance, reported that the odors of the alkyl pyrazines are generally associated with pleasant roasted

 0272-2666/95/0005-0063$04.00/0

food (such as chocolate, coffee, roasted nuts), whereas the odors of alkyl pyridines are less pleasant, more amine-like.

Moreover, the sensory properties of strong-smelling (intense) trace constituents are dependent on the media in which the properties are determined. The odor/flavor characters and threshold values of several series of compounds will be discussed in more detail below. Each set of threshold values presented is the result of work by multiple research groups using similar methods. We exclude from the set any results based on alternate methods.

Aliphatic Nitrogen Compounds

Relatively little is known about the sensory properties of natural aliphatic nitrogen compounds. These compounds, which have been found in flower scents,[10] include amino acid derivatives and degradation products. For instance, from leucine there are oxime, nitrile and nitro derivatives. The odor qualities of these compounds resemble the odor qualities of the corresponding aldehydes, alcohols and ethers. Table I shows the odor/flavor threshold values of nitro-compounds and nitriles in water and other media. The lowest values obtained were for 2'-aminoacetophenone.

Aromatic Nitrogen Compounds

These compounds occur in highest concentration and most frequently in natural isolates. The most important representatives of this group are indole and methyl anthranilate, whose odors are well known. Indole has an animal, fecal odor in higher concentration (>0.1% in diethyl phthalate); in lower concentration its odor character turns to aromatic floral. Methyl anthranilate and its homologues and analogues have citrusy odor notes more or less resembling mandarin. Methyl anthranilate itself is a character-impact compound in mandarin and tangerine oils.[10]

2'-Aminobenzaldehyde, 2'-aminoacetophenone, phenylacetaldoxime, phenylacetonitrile, 1-nitro-2-phenylethane all have aromatic floral and somewhat spicy odor characteristics.[10]

In Table IIa, odor threshold values of benzenoid nitrogen compounds in air are shown. Table IIb gives the odor/flavor threshold values for benzenoid nitrogen compounds in water. In water, skatole has lower threshold values than indole. In Table IIc, the odor/flavor threshold values of benzenoid nitrogen compounds in other media are shown. This time there are no real differences between skatole and indole. Data from Yoshida and Takagi [57-59] are not reported here.

Table I. Odor/flavor threshold values of aliphatic and aromatic nitrogen compounds in water and other media (ppm)

	Odor threshold in water[11-16]	Flavor threshold in skim milk[17]	Flavor threshold in beer[18]
2-methyl-1-nitropropane	5	-	-
3-methyl-1-nitrobutane	0.15	-	-
1-nitro-2-phenylethane	0.002	-	-
3-methylbutanenitrile *	1	-	-
phenylacetonitrile**	1	-	-
2'-aminoacetophenone	0.0002	0.0004	0.005
4'-aminoacetophenone	100	-	-

* isobutyl cyanide
** benzyl cyanide

Table IIa. Odor threshold values of benzenoid nitrogen compounds in air (mg/m³)

	a[19]	b[22]
methyl anthranilate	0.0072	-
indole	0.00015	0.00004
skatole	0.0031	-
quinoline	0.079	-

Pyridines

Pyridine and its lower homologues (up to three carbon atoms) have pungent, diffusive, amine-like, disagreeable odors in higher concentration (>0.1%) in water. Maass and Zablinsky[136] described the odor of 3-butylpyridine as sweet-

Table IIb. Odor/flavor threshold values of benzenoid nitrogen compounds in water (ppm)

	Odor[37]	Odor[38]	Flavor[39]	Flavor[40]	Odor[40]	Odor[41]	Odor[42]	Odor[43,44]	Odor[45]	Odor[46]
methyl anthranilate	0.06	0.003	-	-	-	-	-	-	-	-
N-methyl methyl-anthranilate	-	-	0.02	-	-	-	-	-	-	-
indole	-	-	-	0.5	0.3	0.36	0.3	0.14	-	-
skatole	-	-	-	0.05	0.01	-	-	0.0002	0.05	-
quinoline	-	-	-	-	-	-	-	-	-	0.7

Table IIc. Odor/flavor threshold values of benzenoid nitrogen compounds in media other than water (ppm)

	Odor in diethyl phthalate[47]	Odor in white wine[48]	Flavor in tangerine juice[39]	Flavor in degassed beer[49-51]	Flavor in synthetic butter[52,53]	Odor in aqueous ethanol[54]	Flavor in beer[10,55]	Flavor in sunflower oil[56]
methyl anthranilate	0.44	0.3	-	-	-	-	-	-
N-methyl methyl-anthranilate	-	-	0.16	-	-	-	-	-
indole	9	-	-	0.1	0.02	0.33	-	0.05
skatole	4	-	-	-	0.05	0.14	-	-
ethyl nicotinate	-	-	-	-	-	-	6	-

Table IIIa. Odor descriptions of pyridine derivatives[131]

Substituted pyridine	Odor description
4-isopropenyl-	green-bitter, nutty-beany, slightly sweet
4-isopropenyl-2-methyl-	ether-like, browny-acidy, radish (ozone-like)
2-ethyl-4-isopropyl-	slightly nutty, herbal, bitter
2,4-diisopropenyl-	earthy, slightly seaweed, somewhat citrus
2-isopropyl-4-methyl-	earthy green, somewhat sour and citrus
4-isopropyl-2-methyl-	amine-like, ozonous green, violet perilla
3-[(Z) and (E)-1-buten-1-yl]-	herbal, white floral-like, minty
5-[(Z) and (E)-1-buten-1-yl]2-propyl-	somewhat rose, fermented beany, wormwood
3-[(Z) and (E)-1-buten-1-yl]4-propyl-	earthy green, green beany, powdery, musk-like
3-phenyl-	nutty, roasted soybean, methyl cinnamate-like
4-methyl-3-phenyl-	minty, sweet, fermented earthy
5-phenyl-2-propyl-	green tomato leaf, slightly methyl cinnamate-like
2-acetyl-4-isopropenyl-	grassy, sweet, minty, somewhat amber-like
4-acetyl-2-isopropenyl-	weak herbal green, fermented roast
2-acetyl-4-isopropyl-	grassy-green leaf, green herbal, somewhat violet

Table IIIb. Odor threshold values of pyridines in air (mg/m³)

	a[19]	b[20]	c[21]
pyridine	0.28	0.023	-
2-methyl-	0.17	0.010	-
3,4-dimethyl-	-	0.005	-
3,5-dimethyl-	-	0.005	-
2,6-dimethyl-	-	0.003	-
2-ethyl-	-	-	0.06
5-ethyl-2-methyl-	0.06	-	-
2-propyl-	-	-	0.01
2-butyl-	-	-	0.002
2-pentyl-	-	-	0.0002
2-hexyl-	-	-	0.001

Table IIIc. Odor/flavor threshold values of pyridines in water and other media (ppm)

	Flavor in light ale[79]	Odor in water[80]	Odor in water[81-83]	Flavor in water[84]	Flavor in water[85]
pyridine	-	-	-	-	1-2
2-methyl-	0.2	-	-	-	-
5-ethyl-2-methyl-	-	0.019	-	-	-
2-pentyl-	-	-	0.0006	-	-
2-hexyl-	-	-	-	0.00028	-
2-acetyl-	0.1	-	0.019	-	-

ish, reminiscent of trimethylpyridine. Buttery et al.[9] reported that in dilute water solutions 2-pentylpyridine has a fatty and tallowy odor. According to Thomas and Bassols,[84] trained flavorists describe 3-hexyl-pyridine as having a fatty, citrus, orange note, while 5-hexyl-2-methylpyridine has fatty, fishy, metallic and mandarin notes. Ishihara et al.[131] published odor profiles of synthetic pyridine compounds identified in spearmint oil. Their findings are shown in Table IIIa. The researchers concluded that the nitrogen compounds seem to contribute to the characteristic odor profile of the spearmint oil because of their powerful and pungent aromas.

Ishihara also mentioned that it was reported that 2-acetylpyridine has a strong roasted and coffee-like odor, while that of 2-acetyl-6-methylpyridine is chocolate-like. The researchers reported that 2-acetyl-4-isopropenylpyridine, which is a major component (34%) in the basic fraction of spearmint oil, has a powerful grassy-sweet and minty odor. The odor descriptions of pyridines are shown in Table IIIa and threshold values in Tables IIIb and IIIc.

Table IIIb gives an overview of the known odor threshold values of pyridines and other nitrogen compounds in air. The study of Devos et al.[19] presents a weighted average of the older literature. In more recent literature,[23-35] 12 threshold values for pyridine in air could be found; 8 of 12 authors found a threshold value between 0.1 and 1 mg/m,³ while 2 were above and 2 were below this range. Extensive investigations by Amoore[25] with a total of 205 persons, average value of 2.1 mg/m,³ show a factor of 100 between the most sensitive and most insensitive subjects. Baker and Luh[36] found a factor of around 1,000 between the extremes.

The odor threshold value of pyridine in water has also been extensively investigated.[25,41,42,44-46,60-64] Of ten reported values, the range is from 0.1 to 6 ppm, the average value is about 1-2 ppm. In the literature, the odor threshold value of pyridine in other media has been reported also.[68-78] Nine values are determined in mineral oil and range from 1.5 to 12 ppm, with an average value of about 2-3 ppm. The dozens of publications in the medical literature with data about the odor threshold value of pyridine in water are not reported here. In general these publications show relatively low detection and high recognition threshold values with a ratio of about 1,000.[65-67]

Odor/flavor threshold values of pyridines in water and other media are shown in Table IIIc. The threshold values obtained by Jugel[86] for the bitter taste of some pyridines are not reported.

Pyrazines

In contrast to pyridine derivatives, a lot more is known[10] about the sensory properties of pyrazine derivatives. With respect to their odor quality, some main groups of pyrazine

Table IVa. Odor descriptions of natural pyrazine derivatives[10]

Substituted pyrazine	Odor description
methyl-	earthy, leafy, dusty, roasted nutty, burnt
2,3-dimethyl-	sweet dusty, green, nutty, peanut-like
2,5-dimethyl-	earthy, raw potato, ribes, burnt, cheesy, wheat-like
2,6-dimethyl-	estery, oxidized
ethyl-	buttery, rum, roasted
2-ethyl-3-methyl-	butterscotch, nutty
trimethyl-	estery, creamy, sweetish, cocoa, musty, ashtray, roasted, earthy
tetramethyl-	creamy, sweet, cardboard
2,3-diethyl-	green, grassy, musty, earthy, vegetable
2,6-diethyl-	raw potato
2-ethyl-3,5-dimethyl-	somewhat potato-like, meaty, musty, green
2-ethyl-3,6-dimethyl-	baked potato, earthy, roasty
2,5-diethyl-3-methyl-	earthy, roasty
2-isobutyl-3-methyl-	green (bell pepper), dry and sweet notes
2-isopentyl-3,6-dimethyl-	green

Table IVb. Odor threshold values of pyrazines in air (mg/m³)

	a[87,88]	b[89,90]
methyl-	1.90	-
2,3-dimethyl-	0.90	-
2,5-dimethyl-	0.17	-
2,6-dimethyl-	0.25	-
vinyl-	0.33	-
ethyl-	0.25	-
2-ethyl-3-methyl-	0.15	-
2-ethyl-5-methyl-	0.04	-
trimethyl-	0.19	-
tetramethyl-	0.69	-
(2,3-diethyl-)-	0.05	-
2-ethyl-3,5-dimethyl-	-	0.00001
2-ethyl-3,6-dimethyl-	0.02	0.0025
2,3-diethyl-5-methyl-	0.023	0.000014

derivatives can be distinguished: lower alkyl-substituted (up to five carbon atoms); higher alkyl-substituted (more than five carbon atoms); alkyl- and methoxy-substituted; and other substituents. The odors of lower alkyl-substituted pyrazines are in general described as roasted, herbaceous, nutty and chocolate-like. More specific odor descriptions are: burnt, roasted, brown, chocolate, butterscotch, nutty.[10] The odors of higher alkyl-substituted pyrazines are more earthy and somewhat green, with aromatic and woody notes. The alkyl- and methoxy-substituted pyrazines have strongly green, somewhat earthy odor characteristics with roasted, nutty and floral by-notes.[10] Specific odor descriptions for 2-isobutyl- and 2-sec.butyl-3-methoxypyrazine are the characteristic note of green bell pepper and a clear galbanum oil connotation respectively. The odor descriptions of alkyl-pyrazines are shown in Table IVa and of alkyl-methoxypyrazines in Table IVe.

The threshold values of these pyrazines are revealed in Tables IVb-d, f-h. Table IVb shows the known odor threshold values of pyrazines in air. The ratio between values for the same compound obtained by different investigators can be as large as a factor of 1,000.

In Table IVf, the threshold values of the methoxypyrazines in air are presented. Table IVb shows threshold values of substituted pyrazines in air.

Table IVc shows the odor/flavor threshold values of substituted pyrazines in water. Not shown is the value from a report by Buttery et al.[44] mentioning a threshold value of 0.06 ppm for methylpyrazine. This is probably a transcription error (ppb instead of ppm). Not reported here are the bitter taste threshold values determined by Jugel[86] for some substituted pyrazines.

Table IVd presents the odor/flavor threshold values of pyrazines in media other than water. Again in Tables IVc and IVd one can see striking differences among the results of different investigators.

Table IVc. Odor/flavor threshold values of pyrazines in water (ppm)

	Odor[95]	Odor[81,96-98]	Odor[99-101]	Odor[102-103]	Flavor[104]	Flavor[105]	Odor[106]	Flavor[106]	Odor[107]
methyl-	105	60	100	30	0.25	-	-	-	-
2,3-dimethyl-	-	2.5	0.4	0.8	0.1	-	-	-	-
2,5-dimethyl-	35	1.75	-	0.08	0.02	1	-	-	-
2,6-dimethyl-	54	1.5	-	0.4	-	-	-	-	-
ethyl-	22	6.0	-	4.0	-	-	-	-	-
2-ethyl-5-methyl-	-	0.1	-	0.016	-	-	-	-	-
2-ethyl-6-methyl-	-	-	-	0.04	-	-	-	-	-
trimethyl-	9	-	0.4	-	0.01	-	-	-	-
tetramethyl-	10	-	1.0	-	-	-	-	-	-
2,5-diethyl-	-	0.02	-	-	-	-	-	-	-
2,6-diethyl-	-	0.006	-	-	-	-	-	-	-
2-ethyl-3,5-dimethyl-	15	0.001	-	-	-	-	0.002	0.00025	-
2-ethyl-3,6-dimethyl-	43	0.0004	-	-	-	-	-	-	-
2,3-diethyl-	-	-	-	-	-	-	0.001	0.00005	-
5-methyl-2-isobutyl-3-methyl-	-	0.035	-	-	-	-	-	-	0.13
acetyl-	-	0.062	-	-	-	-	-	-	-

Tables IVf, g and h present the odor/flavor threshold values of methoxypyrazines in air, water and other media, respectively.

In general the alkylmethoxypyrazines have lower threshold values than the alkyl-substituted pyrazines. The substitution of a methyl group by a methoxy group lowers the threshold value by a factor of 1,000.

In alkyl-substituted methoxypyrazines one can notice that branching of a relatively small (C_4-C_5) carbon chain near a polar group strongly influences (decreases) the threshold value of the volatile compound. The same holds true for alkylthiols.[137]

Table IVd. Odor/flavor threshold values of pyrazines in media other than water (ppm)

	Odor in paraffin oil[95]	Odor in vegetable oil[97]	Flavor in dark beer[108]	Flavor in light ale[79]	Flavor in emulsion[104]	Flavor in oil[105]	Odor in sunflower oil[121]
methyl-	27	-	100	1	0.2	-	-
2,3-dimethyl-	-	-	50	0.02	0.5	-	-
2,5-dimethyl-	17	2.6	25	0.05	0.03	2	-
2,6-dimethyl-	8	-	3	0.1	-	-	-
ethyl-	17	-	10	-	-	-	-
2-ethyl-5-methyl-	-	0.32	1	-	-	-	-
trimethyl-	27	-	1	0.1	0.022	-	-
tetramethyl-	38	-	>100	0.2	-	-	-
2,5-diethyl-	-	0.27	-	-	-	-	-
2-ethyl-3,5-dimethyl-	24	-	0.005	0.05	-	-	0.003
2-ethyl-3,6-dimethyl-	24	0.024	0.025	0.05	-	-	-
acetyl-	-	-	-	-	-	-	0.01

Thiazole Derivatives

The odor qualities of substituted thiazoles have been described in detail by Ho and Jin.[132]

Pittet and Huzra[128] stated that the low 2-alkylthiazoles have green, vegetable-like odors.

Buttery et al.[133] reported that some 4,5-dialkylthiazoles pos-sessed potent bell pep-per aroma.

Viani et al.[134] reported that 2-isobutylthiazole occurred in tomato and that it possessed a strong green odor resembling that of tomato leaf. Table V shows the odor/flavor threshold values of thiazoles in water and other media.

Structure-Activity Relationships

By studying structure-activity relationships in olfaction one tries to correlate molecular parameters with sensory properties. The molecular parameters often are physicochemical properties derived from the "electronicity" and the "stereocity" of the molecule. "Electronicity" means the complete electronic charge distribution over the whole molecule. "Stereocity" can be defined as the size, shape, volume and profile of the molecule. The sensory properties of the compounds can, for instance, concern qualitative odor and flavor descriptions, odor and flavor threshold

Table IVe. Odor descriptions of natural methoxypyrazines[10]

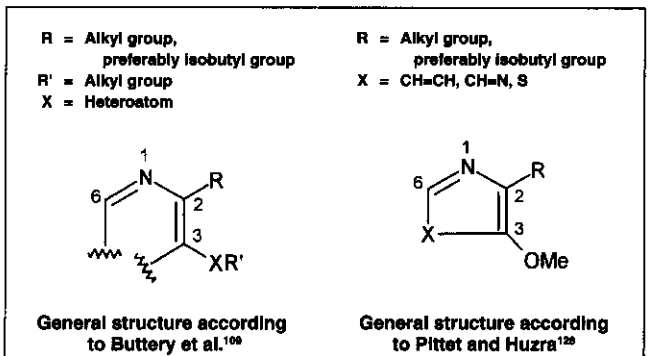
Substituted pyrazine	Odor description
2-methoxy-3-methyl-	popcorn, potatoes, roasted peanuts, chocolate-like
2-isopropyl-3-methoxy-	strong galbanum-like, earthy, musty, potato bin, green pepper, roasted
2-isobutyl-3-methoxy-	strongly green (bell pepper), musty, earthy
2-sec.butyl-3-methoxy-	green (peas, bell pepper, galbanum)
2-isopropyl-3-methoxy-6-methyl	strongly green (bean), floral and ethereal undertone; no nutty notes
2,6-dimethoxy-3-isopropyl-5-methyl-	nutty, green (bell pepper), woody by-note
acetyl-	breadcrust, nutty, reminiscent of acetamide, chimney soot
2-acetyl-3-methoxy-6-methyl-	weak, breadcrust, green, musky note, chimney soot
2-(alpha-hydroxyiso-propyl) -3-methoxy-5-methyl-	weak, green (bell pepper), earthy note, chimney soot

values in air or other media, quantitative intensity ratings, odor-similarity ratings and preference ratings, and the slopes according to Stevens' power law.

One can investigate simple qualitative structure-activity relationships. For example, one might ask, "Which parameters have molecules with a green bell pepper odor character in common?" One can also study more complicated quantitative structure-activity relationships (QSAR) by correlating a molecule's defined molecular parameters (such as molecular volume or dipole moments) with measured threshold values of the molecule. In QSAR studies one has to realize that for a given chemical compound the molecular parameters may be well defined, whereas the measured individual threshold values for the same compound within a group of observers can vary by a factor of 100 or even more.[25] Simple general structures for chemical compounds with green bell pepper odor have been proposed by Buttery et al.[109] and by Pittet and Huzra.[128] These structures are shown in Figure 1.

Table IVf. Odor threshold values of methoxypyrazines in air (ng/m³)

	a[91]	b[92]	c[93]	d[94]
2-isopropyl-3-methoxy-	3.6	< 3	0.75	5
2-isobutyl-3-methoxy-	-	-	3	5



General structure according to Buttery et al.[109]

General structure according to Pittet and Huzra[128]

Figure 1. Structures of compounds with green bell pepper odor

Masuda and Mihara[102] suggested a receptor site interaction model for 2-methoxyalkylpyrazines as demonstrated in Figure 2. Rognon and Chastrette[129] recently made a thorough investigation of structure-odor relationships of nitrogen compounds with bell pepper aroma. They proposed a highly predictive tridimensional interaction model for the bell pepper note (see Figure 2). The threshold values in water for pyridines can vary from 1-2 ppm for pyridine to 0.019 ppm for 5-ethyl-2-methylpyridine, 0.0006 ppm for 2-pentylpyridine and 0.00028 ppm for 2-hexylpyridine (Table IIIc).

If one compares the threshold values determined by the same scientists one can notice that, for instance, these values in water for substituted pyrazines can vary from 60 ppm for methylpyrazine to 0.1 ppm for 2-ethyl-5-methylpyrazine and 0.0004 ppm for 2-ethyl-3,6-dimethylpyrazine (see Table IVc). The values found for alkyl-methoxypyrazines are significantly lower; they can vary from 4 ppb for 2-

Table IVg. Odor/flavor threshold values of methoxypyrazines in water (ppb)

	Odor[15,51,85,91,96,108,113]	Odor [100,101]	Odor[102,103,114]	Odor[107]	Flavor[115]	Flavor[116]
2-methoxy-3-methyl-	4	3	7	-	-	-
2-isopropyl-3-methoxy-	0.002	10	0.024	-	0.001	-
2-isobutyl-3-methoxy-	0.002	10	0.045	0.016	-	0.01
2-sec.butyl-3-methoxy-	0.002	-	0.04	-	0.001	-
(S)-(+)-2-sec.butyl-3-methoxy-	-	-	0.10	-	-	-
(R)-(−)-2-sec.butyl-3-methoxy-	-	-	0.01	-	-	-
2-isopropyl-3-methoxy-6-methyl-	-	-	-	0.05	-	-

Table IVh. Odor/flavor threshold values of methoxypyrazines in media other than water (ppb)

	Flavor threshold in mashed potatoes[117]	Odor threshold in diethyl phthalate[118]	Odor threshold in model wine[119]	Odor threshold in red wine[119]	Flavor threshold in model wine[119]	Flavor threshold in red wine[119]	Odor threshold in blanc wine[120]	Odor threshold in mineral oil[121]	Odor threshold in sunflower oil[58]	Flavor threshold in sunflower oil[58]
2-methoxy-3-methyl-	50	-	-	-	-	-	-	-	-	-
2-isopropyl-3-methoxy-	86	0.01	0.002	0.002	0.002	0.002	0.002	-	-	-
2-isobutyl-3-methoxy-	-	-	0.002	0.016	0.002	0.002	0.001	2	-	-
2-sec.butyl-3-methoxy-	-	-	-	-	-	-	-	-	0.5	0.3

methoxy-3-methylpyrazine down to 0.002 ppb for 2-isobutyl-3-methoxypyrazine (Table IVg).

From these figures one may conclude that there is a strong influence of the alkyl substituent(s) in cyclic nitrogen compounds on the threshold values of these compounds. It is general knowledge[19,130] that in homologous series, such as alkanes, alcohols, alkanals and alkanoic acids, the threshold value goes through a minimum by lengthening of the carbon chain. It seems that in the interaction of the stimulus with the receptor site, there exists an optimal sterical fit.

Sometimes one tries to replace an odorant molecule having certain sensory properties with a different molecule because the former has some undesirable physicochemical properties. For instance, indole can discolor with other compounds in perfume compositions. Therefore the chemical compound dihydroindenyl-2,4-dioxane (formaldehyde indan-1-ol-2-hydroxymethyl acetal) was developed and is commercially available under the names Indoflor krist (H&R), Indolal (Dragoco) and Indolarome (IFF). The dihydroindenyl-2,4-dioxane molecule resembles indole somewhat, sterically; however, the polar part of the molecule (i.e., a dioxane instead of a nitrogen) is quite different.

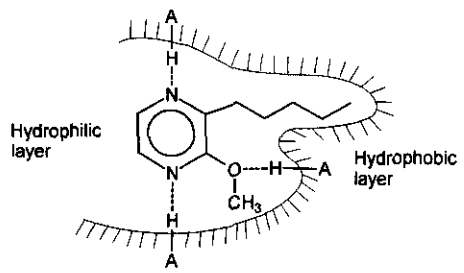
The "electronicity" of odorant molecules is often determined by electron-releasing or by electron-attracting atoms or atom groups in the molecule. Nitrogen compounds are polar (basic) because the nitrogen atom possesses a lone electron pair, which easily attracts free protons. Some oxygen compounds, like carbonyls and ethers, can form hydrogen bridges within a single molecule or with other molecules. The polar atoms may give rise to the formation of hydrogen bridges with the receptor sites for sweet-tasting compounds as proposed by Shallenberger[137] and for the green bell pepper odor of alkyl-methoxypyrazines as suggested by Masuda and Mihara[102] and shown in Figure 2.

However, one should be careful with the interpretation of the influence of heteroatoms in odorant molecules. One can come to different conclusions with the same molecule. By comparing substituted pyridines with substituted pyrazines, Rognon and Chastrette[129] concluded, contrary to Masuda and Mihara,[102] that only one nitrogen atom was involved in the interactions with the receptor sites (see Figure 1).

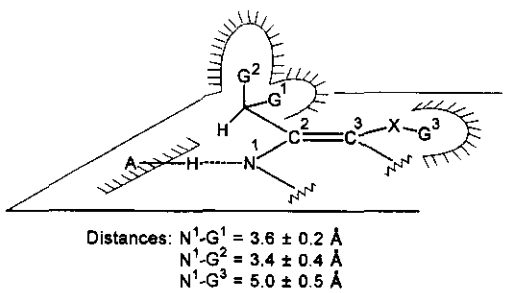
An interesting example of the influence of the formation of hydrogen bridges on the threshold value is found in the molecules of aminoacetophenones. The most volatile 2'-aminoacetophenone can form an intermolecular hydrogen bridge and has a threshold value of 0.0002 ppm in water, whereas the molecules of the less volatile 4'-aminoacetophenone form intramolecular hydrogen bridges and this compound has a threshold value of 100 ppm in water

Table V. Odor/flavor threshold values of thiazoles in water and other media (ppm)

	Odor threshold in water[11-13,44,122]	Odor threshold in water[123]	Flavor threshold in water[124]	Flavor threshold in water[125]	Flavor threshold in water[126]	Odor threshold in model solution[127]	Odor threshold in red wine[127]	Odor threshold in white wine[127]
2-isobutyl-thiazole	0.0035	-	0.002	0.0013	0.003	0.050	0.20	0.35
benzo-thiazole	0.08	0.08	-	-	-	-	-	-



Interaction model according to Masuda and Mihara[102]



Interaction model according to Rognon and Chastrette[129]

Figure 2. Interaction models for compounds with bell pepper odor

(Table I). In studying quantitative structure-activity relationships one has to give a proper expression to the activity. In pharmaco-chemistry it is usual to express the activity as log 1/C, which is the negative logarithm of the minimum activity concentration of the chemical compound. In sensory analysis of threshold values this term has been proposed by Devos et al.[19] as p(Ol). Thus, for a threshold value of 1 part per thousand, the p(Ol) = 3; for 1 ppm, p(Ol) = 6; for 1 ppb, p(Ol) = 9. With this term one can get simple equations for the calculations of structure-activity relationships. For example: p(Ol) = f(Dielectrical constant) + f(Molecular volume) + constant. With this formula one can carry out multiple regression analyses and find a certain correlation coefficient and investigate which molecular parameters are important for the given sensory property.

Concluding Remarks

After studying the sensory properties of volatile nitrogen compounds, one can make the following concluding remarks with respect to their structure-activity relationships.

- Whereas the molecular parameters of a volatile compound can be well defined, its sensory properties often possess a great uncertainty. Therefore, straightforward conclusions regarding their structure-activity often can not be drawn.
- Volatile nitrogen compounds with similar molecular volume, shape and profile (so-called isosteric molecules), such as compounds with green bell pepper odor, can possess reminiscent sensory qualities.

- Threshold values can be strongly influenced by the potential of the odorous molecules to form inter- or intramolecular associations (for example, by hydrogen bridges).
- Homologous series of volatile nitrogen compounds with a straight aliphatic side chain show a dip in their threshold values with a certain chain length. Minimum threshold values are found with a chain length of 6 to 7 carbon atoms.
- In volatile heterocyclic nitrogen compounds a methoxy group can strongly decrease the threshold value of the compounds.

References

Address correspondence to Mans H. Boelens, Boelens Aroma Chemical Information Service, Groen van Prinstererlaan 21, 1272 GB, Huizen, The Netherlands.

1. JA Maga, *J Agric Food Chem* **21** 22-30 (1973); *CRC Crit Rev Food Technol* **10** 373-403 (1978); *J Agric Food Chem* **29** 895-898 (1981)
2. G Vernin, *Perf & Flav* **7**(5) 23 (1982)
3. A Gallois, *Sci Aliment* **4** 145-166 (1984)
4. H Maarse et al, *Volatile Compounds in Food*, The Netherlands: TNO Biotechnology and Chemistry Institute (1989-1994)
5. I Flament, in *Volatile Compounds in Foods and Beverages*, H Maarse, ed, New York: Marcel Dekker (1991) pp 617-670
6. T Yamanishi, in *Flavor Research: Recent Advances*, R Teranishi, R Flath and H Sugisawa, eds, New York: Marcel Dekker (1981) pp 231-304
7. I Flament, in *Coll Int Aromes Aliment*, J Adda, ed, Paris: Lavoisier (1982) pp 82-105
8. C Bicchi, *Flavour Fragr J* **2** 29 (1987); **3** 143-153 (1988)
9. RG Buttery et al, *J Agric Food Chem* **26** 1227-1229 (1977)
10. MH Boelens and LJ van Gemert, *Perf & Flav* **19**(5) 51-65 (1994)
11. RG Buttery et al, *J Agric Food Chem* **35** 540-544 (1987)
12. RG Buttery et al, in *Flavor Chemistry: Trends and Developments*, R Teranishi et al, eds, ACS Symposium series 338, Washington, DC: American Chemical Society (1989) pp 213-222
13. RG Buttery et al, *J Agric Food Chem* **38** 336-340 (1990)
14. RG Buttery et al, *J Agric Food Chem* **38** 792-795 (1990)
15. RG Buttery, in *Flavor Science; Sensible Principles and Techniques*, TE Acree and R Teranishi, eds, Washington, DC: American Chemical Society (1993) pp 259-286
16. RG Buttery and L Ling, *J Agric Food Chem* **42** 1-2 (1994)
17. OW Parks et al, *Nature* **202** 185-187 (1964)
18. MC Meilgaard, *Master Brew Assoc Am Tech Quart* **12** 151-168 (1975)
19. M Devos et al, *Standardized Human Olfactory Thresholds*, Oxford: IRL Press (1990)
20. Y Moriguchi et al, in *Proceedings VIth World Congress on Air Quality, Paris, May 1983*, vol 2, Paris (1984) pp 393-399
21. P Schieberle, in *Progress in Flavour Precursor Studies*, P Schreier and P Winterhalter, eds, Carol Stream, IL, USA: Allured Publishing (1993) pp 343-360
22. F Etzweiler et al, *Seife-Ole-Fette-Wachse* **106** 419-427 (1980)
23. H Bahnmuller, in *Proceedings VIth World Congress on Air Quality, Paris, May 1983*, vol 2, Paris (1984) pp 417-422
24. R Ahlstroem et al, *Scand J Work Environ Health* **12** 574-581 (1986)
25. JE Amoore, *J Am Water Works Assoc* **78** 70-76 (1986)
26. JA Don, paper presented at "Odour Control in Industry," London, Mar 18, 1986

27. P den Hartigh, *VDI-Berichte* **56** 277-287 (1986)
28. P MacLeod et al, *VDI-Berichte* **56** 271-275 (1986)
29. WS Cain et al, *Am Ind Hyg Assoc J* **48** 47-55 (1987)
30. JC Stevens et al, *Chem Senses* **13** 643-653 (1988)
31. JE Cometto-Muniz and WS Cain, *Physiol Behav* **48** 719-725 (1990)
32. JE Cometto-Muniz, Personal communication to LJ van Gemert (1993)
33. WS Cain and JF Gent, *J Exp Psychol Hum Percept Perform* **17** 382-391 (1991)
34. M Laska and R Hudson, *Chem Senses* **16** 651-662 (1991)
35. B Berglund and HS Esfandabad, Abstracts Xth Congress of ECRO, Munich, Aug 1992
36. RA Baker and M-D Luh, *Sci Total Environ* **2** 13-20 (1973)
37. L Appell, *Am Perfum Cosmet* **84**(3) 45-50 (1969)
38. T Hirvi and E Honkanen, *Z Lebensm Unters Forsch* **175** 113-116 (1982)
39. CW Wilson and PE Shaw, *J Agric Food Chem* 29 494-496 (1981)
40. F Dietz and J Traud, *GWF-Wasser/Abwasser* **119** 318-325 (1978)
41. J Le Magnen, *Arch Sci Physiol* **6** 125-160 (1952)
42. J Holluta, *Gas Wasserfach* **101** 1018-1023 (1960)
43. RG Buttery et al, *J Agric Food Chem* **27** 646-647 (1979)
44. RG Buttery et al, *J Agric Food Chem* **36** 1006-1009 (1988)
45. M Kauffmann, *Z Sinnesphysiol* **42** 271-280 (1907)
46. RA Baker, *J Am Water Works Assoc* **55** 913-916 (1963)
47. A Rosenthal, *Riechstoffind* 142-143, 150-151, 161-162 (1927)
48. RR Nelson et al, *J Food Sci* **42** 57-59 (1977)
49. GAF Harrison, *Proc Europ Brew Conv,* Brussels (1963) pp 247-256
50. GAF Harrison, *Brewers Digest* 74-76 (Jun 1967)
51. GAF Harrison and E Collins, *Proc Am Soc Brew Chem* 83-87 (1968)
52. G Urbach et al, *Rep 18th Int Dairy Congress* (1970) p 234
53. G Urbach et al, *J Dairy Res* **39** 35-47 (1972)
54. DMH Thomson, in *Progress in Flavour Research,* J Adda, ed, Amsterdam: Elsevier (1984) pp 97-101
55. MC Meilgaard, in *Geruchs- und Geschmacksstoffe,* F Drawert, ed, Nurnberg: Verlag Hans Carl (1975) pp 211-254
56. M Preininger and W Grosch, *Lebensm Wiss Technol* **27** 237-244 (1994)
57. M Yoshida, *Jap Psychol Res* **14** 101-108 (1972)
58. M Yoshida, *Bull Facul Sci Eng Chuo Univ* **27** 343-353 (1984)
59. SF Takagi, *Chem Senses* **14** 24-46 (1989)
60. RW Moncrieff, *Am J Physiol* **70** 1-20 (1957)
61. JE Amoore et al, *J Chem Ecol* **1** 299-310 (1975)
62. AH Sherman et al, *Otolaryngol Head Neck Surg* **87** 717-733 (1979)
63. MD Rabin and WS Cain, *Percept Psychophys* **39** 281-286 (1986)
64. RG Buttery et al, *J Agric Food Chem* **42** 791-795 (1994)
65. RI Henkin and FC Bartter, *J Clin Invest* **45** 1631-1639 (1966)
66. RI Henkin, *Perf & Flav* **1**(3) 19-25 (1976)
67. HJ Vreman et al, *Nephron* **26** 163-170 (1980)
68. HS Koelega and EP Koester, *Ann N Y Acad Sci* **237** 234-246 (1974)
69. MS Pollack et al, *Immunogen* **15** 577-589 (1982)
70. RJ Hyde et al, *J Dent Res* **60** 1730-1734 (1981)
71. JE Amoore and BG Ollman, *Rhinol* **21** 49-54 (1983)
72. CJ Wysocki and GK Beauchamp, *Proc Nat Acad Sci USA* **81** 4899-4902 (1984)
73. S Satya-Murti and EA Crisostomo, *Muscle Nerve* **11** 406-407 (1988)

74. E Koss et al, *Lancet* 622 (1987)
75. E Koss et al, *Neurol* **38** 1228-1232 (1988)
76. BJ Cowart, *Ann N Y Acad Sci* **561** 39-55 (1989)
77. KM Dorries et al, *Develop Psychobiol* **22** 423-427 (1989)
78. CJ Wysocki et al, *Proc Nat Acad Sci USA* **86** 7976-7978 (1989)
79. RJ Harding et al, *J Sci Food Agric* **28** 225-232 (1977)
80. AA Rosen et al, *J Water Pollut Control Fed* **35** 777-782 (1963)
81. R Teranishi et al, in *Geruchs- und Geschmacksstoffe*, F. Drawert, ed, Nurnberg: Verlag Hans Carl (1975) pp 177-186
82. RG Buttery et al, *J Agric Food Chem* **25** 1227-1229 (1977)
83. RG Buttery, in *Flavor Research: Recent Advances*, R Teranishi et al, eds, New York: Marcel Dekker (1981) pp 175-216
84. AF Thomas and F Bassols, *J Agric Food Chem* **40** 2236-2243 (1992)
85. M Rothe et al, *Nahrung* **16** 483-495 (1972)
86. H Jugel, Thesis, Technical Univ Munich, 1979
87. SM Fors, in *Progress in Flavour Research*, J Adda, ed, Amsterdam: Elsevier (1984) pp 29-34
88. SM Fors and BK Olofsson, *Chem Senses* **10** 287-296 (1985)
89. C Cerny, Private communication, in I Blank et al, *Z Lebensm Unters Forsch* **195** 239-245 (1992)
90. C Cerny and W Grosch, *Z Lebensm Unters Forsch* **198** 210-214 (1994)
91. RG Buttery et al, *J Agric Food Chem* **17** 1322-1327 (1969)
92. R Savenhead et al, *J Chrom* **328** 219-231 (1985)
93. I Blank et al, *Z Lebensm Unters Forsch* **195** 239-245 (1992)
94. D Khiari et al, *Water Sci Technol* **25** 97-104 (1992)
95. PE Koehler et al, *J Food Sci* **36** 816-818 (1971)
96. RM Seifert et al, *J Agric Food Chem* **18** 246-249 (1970)
97. DG Guadagni et al, *J Sci Food Agric* **23** 1435-1444 (1972)
98. DG Guadagni, Unpublished work, in RG Buttery et al, *J Sci Food Agric* **24** 1125-1131 (1973)
99. PJ Calabretta, Food Manufacture Ingredient Survey (Mar 1973) pp 7-8, 10
100. PJ Calabretta, *Cosm & Perf* **90**(6) 74-80 (1975)
101. PJ Calabretta, *Perf & Flav* **3**(3) 33-34, 36, 40-42 (1978)
102. H Masuda and S Mihara, *J Agric Food Chem* **36** 584-587 (1988)
103. S Mihara and H Masuda, *J Agric Food Chem* **36** 1242-1247 (1988)
104. T Shibamoto et al, in *The Analysis and Control of Less Desirable Flavors in Foods and Beverages*, New York: Academic Press (1980) pp 241-265
105. RE Deck and SS Chang, *Chem Ind* 1343-1344 (1965)
106. C Cerny and W Grosch, *Z Lebensm Unters Forsch* **196** 417-422 (1993)
107. HJ Takken et al, *J Agric Food Chem* **23** 638-642 (1975)
108. E Collins, *J Agric Food Chem* **19** 533-535 (1971)
109. RG Buttery et al, *Chem Ind* 490-491 (1969)
110. DG Guadagni, Private communication (1969) to R Teranishi, in *Flavor Chemistry of Lipid Foods*, D Min and TH Smouse, eds, Champaign: The American Oil Chemists' Society (1989) pp 13-25
111. DG Guadagni, Private communication (1970) to R Teranishi, in *Gustation and Olfaction*, London: Academic Press (1971) pp 165-177
112. RM Seifert et al, *J Agric Food Chem* **20** 135-137 (1972)
113. R Teranishi et al, *Ann N Y Acad Sci* **237** 209-216 (1974)
114. S Mihara et al, *J Agric Food Chem* **38** 465-467 (1990)
115. KE Murray et al, *Chem Ind* 897-898 (1970)
116. M Rothe, *Nahrung* **20** 259-266 (1976)
117. DG Guadagni et al, *J Food Sci* **36** 363-366 (1971)
118. U Harder, *Chem Z* **99**(2) 54-69 (1975)
119. JA Maga, in *Flavor and Off-Flavors*, G Charalambous, ed, Amsterdam: Elsevier (1990) pp 61-70
120. MS Allen et al, *Am J Enol Vitic* **42** 109-112 (1991)
121. DA Stevens and RJ O'Connell, *Chem Senses* **16** 57-67 (1991)
122. RG Buttery et al, *J Agric Food Chem* **19** 524-529 (1971)
123. DA Lillard and JJ Powers, EPA-660/4-75-002 (1975)
124. SJ Kazeniac and RM Hall, *J Food Sci* **35** 519-530 (1970)
125. MA Stevens, *J Am Soc Hort Sci* **95** 9-13 (1970)
126. L Schutte, *CRC Crit Rev Food Technol* **4** 457-505 (1974)
127. P Chatonnet et al, *Sci Aliments* **12** 513-532 (1992)
128. AO Pittet and DE Huzra, *J Agric Food Chem* **22** 264-267 (1974)
129. C Rognon and M Chastrette, *Eur J Med Chem* **29** 595-608 (1994)
130. LJ van Gemert and AH Nettenbreijer, *Compilation of Odour Threshold Values in Air and Water*, Central Institute for Nutrition and Food Research TNO, Zeist, The Netherlands, and National Institute for Water Supply, Voorburg, The Netherlands (1977)
131. M Ishihara et al, *J Agric Food Chem* **40** 1647-1655 (1992)
132. CT Ho and QZ Jin, *Perf & Flav* **9**(6) 15-18 (1984)
133. RG Buttery et al, *J Agric Food Chem* **24** 1-3 (1976)
134. R Viani et al, *Helv Chim Acta* **52** 887 (1969)
135. L Buck and R Axel, *Cell* **65** 175-187 (1991)
136. E Maass and K Zablinski, *Ber Dtsch Chem Ges* **47** 1164-1173 (1914)
137. MH Boelens and LJ van Gemert, *Perf & Flav* **18**(3) 29-39 (1993).