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Influence of the chemical structure on the odor qualities and odor thresholds of guaiacol-derived odorants, Part 1: Alkylated, alkenylated and methoxylated derivatives

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ABSTRACT

Guaiacol and its derivatives are commonly found in nature and are known for their characteristic smoky, clove-like and vanilla-like smells. However, there is no systematic investigation of the smell properties of structurally related guaiacol derivatives. In order to establish a comprehensive database on this olfactorily interesting substance class, odor thresholds in air and odor qualities of guaiacol and its alkylated, alkenylated, and methoxylated derivatives were determined by means of gas chromatography-olfactometry. All compounds elicited characteristic smoky/smoked ham-like, vanilla-like/sweet and/or clove-like smell impressions. The odor thresholds of the compounds were generally very low, ranging from 0.00018 to 111 ng/L_{air}. The lowest thresholds were determined for 5-methoxyguaiacol and guaiacol, followed by 4-ethyl- and 4-vinylguaiacol. Some inter-individual differences in the threshold values between panelists were observed, with highest variation in the individual values of *cis*-6-propenyl-, *trans*-6-propenyl- and 3-vinylguaiacol. The smell impressions, on the other hand, were quite consistent.

1. Introduction

One main component of the resin of *Guaiacum* is 2-methoxyphenol (trivial name: guaiacol), which was extracted for the first time via distillation as a pure substance in 1829 by Otto Unverdorben (Unverdorben, 1829). The resin is produced by different species of the genus *Guaiacum*; most common are *G. officinale* and *G. sanctum*. The name Guaiacum can be traced back to the indigenous people term for the plant of the Zygophyllaceae-family which grows in Middle- and South America (Pahlow, 2013).

Guaiacol and its derivatives are widely spread in flora and fauna, and are used as aromatizing agents in the food and perfume industry, but also as antiseptics and local anesthetics in medicine, and as insecticides.

Diverse guaiacol derivatives have been recorded in the condensate of cigarette smoke, as a result of tobacco combustion (Arnarp et al., 1989). The smoky smelling guaiacol also contributes to the aroma of smoked and roasted foods like bacon and coffee, similarly originating from pyrolytic processes, and is a constituent of liquid smoke, which is added to many foods as a flavorant. Examples of literature reports are provided in the Supplementary material.

Guaiacol is also bio-synthesized by insects or several plants, especially *Guaiacum* species as specified in the Supplementary

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material section. However, industrial production of guaiacol involves synthetic routes as the natural sources commonly comprise protected species. Thereby, technical production relies on the methylation of catechol (Fiege et al., 2000). Guaiacol may serve as the starter compound in the synthesis of vanillin (Esposito et al., 1997).

4-Ethyl-, 4-vinyl-, 4-allyl- and 5-propylguaiacol are derivatives that contribute to the aroma of smoked foods and have been, amongst others, identified in smoked ham (Baloga, Reineccius, & Miller, 1990). However, smoking processes are not the only premise for introduction of these compounds into foods. Several processed foods and beverages contain diverse guaiacol derivatives; for example, guaiacol and 4-vinylguaiacol have been identified as aroma compounds in wheat beers, whereas 4-ethyl-, 4-allyl- and 4-vinylguaiacol were found to be important aroma compounds in brandy, demonstrating the importance of *para*-substituted derivatives of guaiacol in the complex world of smell. A table summarizing previous reports about these substances in foods and other consumables is provided in the Supplementary material (Table S1).

Moreover, guaiacol derivatives are widespread in flora and fauna. Plants from all kinds of genera and families produce these substances all over the world. The most common derivative is eugenol (4-allylguaiacol), known, amongst others, as the main component of clove oil (Bhuiyan, Begum, Nandi, & Akter, 2010). This substance is used in dental medicine due to its antibacterial, antiphlogistic and analgesic effects (Hunnius, 1997; Jadhav, Khandelwal, Ketkar, & Pisal, 2004). Another constituent of clove oil is isoeugenol (4-(1-propenyl)-guaiacol) that has been reported to be formed during microbial deterioration processes (Koeduka et al., 2006). Traditional Chinese medicine uses *Mosla chinensis* for pain treatment, which contains *o*-eugenol (6-allylguaiacol), besides its 4-isomer *p*-eugenol (Cao, Li, & Chen, 2011).

5-Allylguaiacol, also known as chavibetol, is biosynthesized by different plants. It is extracted from leaves of *Pimenta pseudocaryophyllus*, which is traditionally used in Brazil in the production of beverages and rum, due to its aromatic odor (Dos Santos, da Silva, Guerrero, Leitão, & Barata, 2009). Apart from that, the antioxidative effect of the extract of leaves of the indigenous *Piper betel* has been attributed to chavibetol, in addition to other substances (Rathee, Patro, Mula, Gamre, & Chattopadhyay, 2006). In the same study the odor of chavibetol was described as "unusual" and exotic, but without any further specifications. In extracts of *Bursera graveolens,* and *Angelica pubescens* as well as *Angelica sinensis*, which are all used in traditional Chinese medicine, 5-methyl- and 4-vinylguaiacol have been identified in minor amounts amongst other compounds (Song, Deng, Wu, & Hu, 2004; Yukawa, Imayoshi, Iwabuchi, Komemushi, & Sawabe, 2006). Other derivatives, namely 4-methyl-, 4-ethyl-, 6-ethyl-, 4-propyl- and 4-allylguaiacol have been identified in two Japanese plant genera (*Larix kaempferi* and *Sasa kurilensis*) (Yasuhara & Sugiura, 1987).

This exemplary selection of bio-synthesized guaiacol derivatives is not to be regarded as comprehensive, as the structures found in flora world-wide are manifold, and, in several species, quite abundant.

In fauna, 5-ethylguaiacol (trivial name: locustol) is a pheromone that is responsible for the swarm formation of locusts, as reported by Nolte et al. in 1973; thereby, this substance was found to be the main component of the assembly-attractant mixture (Nolte, Eggers, & May, 1973). In 2001, Dillon et al. discovered that the formation of this pheromone is caused by intestinal bacteria of the locusts from vegetal material (Dillon, Vennard, & Charnley, 2000).

Despite the numerous reports on prevalence of guaiacol and its derivatives in nature, it is striking that there is no comprehensive investigation of the olfactory properties of individual members of this substance class. To close this gap, the aim of this work was to provide analytical and sensory data on structurally related variants of this scientifically interesting substance class. Accordingly, the aim was to compile comparative data on the absolute odor thresholds in air for a range of guaiacol derivatives, and to systematically record their respective odor qualities. Based on the sensory data, deeper insights into the underlying structure-odor relationships should be elaborated whereas the compiled analytical data should aid future discoveries of compounds belonging to this substance class, which is of such olfactory and chemo-communicative importance.

2. Materials and methods

2.1. Chemicals

Methyl magnesium iodide solution 3M in diethyl ether, palladium on carbon (5%), 2,3-dihydroxybenzaldehyde, dimethylformamide (DMF), iodomethane (CH_3I), methyltriphenylphosphonium bromide, *n*-butyllithium (*n*-BuLi), potassium *tert*-butoxide, hydrochloric acid (HCl), diethyl ether, anhydrous tetrahydrofuran (THF), absolute ethanol (EtOH), magnesium sulfate ($MgSO_4$), and sodium bicarbonate ($NaHCO_3$) were purchased from Sigma-Aldrich (Steinheim, Germany). *n*-Hexane and xylene (dry) were purchased from Acros Organics (Geel, Belgium), Celite® 545, chloroform-d1 ($CDCl_3$) and sodium hydroxide (NaOH) from Carl Roth (Karlsruhe, Germany), and silica gel (Normasil 60, 40–63 μm), ammonium chloride (NH_4Cl), potassium bicarbonate ($KHCO_3$), sodium chloride, anhydrous sodium sulfate (Na_2SO_4), dichloromethane (CH_2Cl_2) and ethyl acetate (EtOAc) from VWR International GmbH (Darmstadt, Germany). 4-Allyl 1,2-dimethoxybenzene (eugenol methyl ether), 3-hydroxy 4-methoxybenzaldehyde (isovanillin), 2-hydroxy 3-methoxybenzaldehyde (*o*-vanillin), 2-methoxy 5-propylphenol (5-propylguaiacol), 2-methoxyphenol (guaiacol), 2-methoxy 6-methylphenol (6-methylguaiacol), 4-ethyl 2-methoxyphenol (4-ethylguaiacol), 4-vinyl 2-methoxyphenol (4-vinylguaiacol), 4-allyl-2-methoxyphenol (4-allylguaiacol, eugenol), 2-allyl 6-methoxyphenol (6-allylguaiacol, *o*-eugenol), and 2,6-dimethoxyphenol (6-methoxyguaiacol, syringol) were purchased from Sigma-Aldrich (Steinheim, Germany). 4-Methyl-2-methoxyphenol (4-methylguaiacol, creosol) was purchased from abcr (Karlsruhe, Germany). 5-Vinyl 2-methoxyphenol (5-vinylguaiacol) was provided by the working group of Professor Schieberle (Technical University of Munich, Munich, Germany). 2,4-Dimethoxyphenol (4-methoxyguaiacol) and 2,5-dimethoxyphenol (5-methoxyguaiacol) were purchased from Activate Scientific (Prien, Germany). All chemicals were used without further purification.

2.2. Nuclear Magnetic Resonance (NMR) spectra

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on an Avance 360 spectrometer, 360 MHz, and Avance 600 spectrometer, 600 MHz (Bruker Biospin, Rheinstetten, Germany) at room temperature at 360 or 600 MHz (^1H), and 90 or 150 MHz (^{13}C), with tetramethylsilane (TMS) as internal standard.

2.3. GC-FID, GC-Olfactometry (GC-O) and GC-Electron Impact-Mass Spectrometry (GC-EI-MS)

GC-FID and GC-O analyses were performed with a Trace GC Ultra (Thermo Fisher Scientific GmbH, Dreieich, Germany) by using the following capillary columns: FFAP (30 m x 0.32 mm fused silica capillary, free fatty acid phase FFAP, 0.25 μm; Chrompack, Mühlheim, Germany) and DB5 (30 m x 0.32 mm fused silica