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The Influence of Molecular Structure on Odor Qualities and Odor Detection Thresholds of Volatile Alkylated Phenols

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Abstract

The relationship between chemical structure and odor characteristics of aroma compounds is interesting in terms of establishing a fundamental understanding and, in the long term, a perspective for the prediction of odor qualities and intensities of unknown compounds; on the other hand, such studies provide a useful tool to analytically elucidate compounds that are exceptionally potent odor contributors to a specific smell. In this respect, a broad knowledge of compounds with regard to their odor threshold and smell specificities compiled in a comprehensive odor library would drastically simplify the chemoanalytical process in identifying aromas and smells. Whereas numerous odor-active substance classes have been investigated intensively, such relationships and fundamental data have hitherto not been established for volatile phenols. In this study, a homologous series and isomers of 30 volatile phenols, including monoalkylated phenols and di- and trimethylphenols, were evaluated by determining their aroma attributes and their odor detection thresholds in air. The investigation demonstrates that the odor qualities, among them leather-like, horse stable–like, and medicinal, as well as the respective threshold values clearly depend on the arrangement of the alkyl substituents at the phenol ring. In particular, phenols with monoalkyl groups in the meta-position were found with very low odor detection thresholds of <1 ng/L air. A comparison of some selected phenols and their corresponding toluenes, which were found to be almost odorless, showed in addition that the phenolic hydroxyl group is obviously an important factor for the odor characteristic of this substance class.

Key words: alkylated phenols, HRGC–olfactometry, odor detection threshold, odor quality

Introduction

The evaluation of odor-active compounds within the volatile fraction of a food results in the identification of a characteristic set of substances responsible for the overall food aroma. Many of these compounds occur in numerous food products and are characterized by high aroma activities. This is the reason that components present in only trace amounts have been identified consistently as important odorants in several foods. One example is the very potent grapefruit juice odorant 1-*p*-menthen-8-thiol. Although the concentration of this thiol in grapefruit juice has been determined to be as low as 0.01 μg/L (10 ng/L), this still has a significant contribution to grapefruit aroma due to its extremely low odor threshold of 0.0001 μg/L water (Buettner and Schieberle 2001b). Another compound, 4-mercapto-4-methylpentan-2-one, has been found to be even more potent, based on both concentration and odor threshold factors in a grapefruit juice matrix (Buettner and Schieberle 2001b). On the other hand, compounds with high odor thresholds can also play an essential role in food aroma when concentrations are high, for example, ethanol in whisky aroma (odor threshold: 24900 μg/L water) (Poisson and Schieberle 2008a). However, a preponderant number of odor-active food compounds have been identified with threshold values in the parts per billion range.

The contribution of a single volatile to the aroma of a food does not depend exclusively on its concentration in the food material itself but also on its odor threshold in the food

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matrix. The respective odor threshold is therefore highly influenced by release parameters of a specific matrix.

The molecular geometry, more specifically the composition and structures of the functional groups within the molecule, is crucial for the perception of an aroma compound. Numerous studies on structure–activity relationships of different substance classes have been carried out, some of them with the final goal of predicting aroma thresholds and qualities of new volatile compounds. For this purpose, systematic approaches have been chosen in an attempt to ascertain the relationships between smell and structure, which at first sight often appear to be chaotic (Kraft et al. 2000; Sell 2006). For example, homologous series and isomers of substance groups have been studied regarding their odor properties by determining odor thresholds and characteristic odor qualities. This has been accomplished, for example, for aliphatic alcohols, carboxylic acids, aldehydes, and esters (Schnabel et al. 1988); aliphatic and aromatic aldehydes (Boelens and van Gemert 1986; von Ranson and Belitz 1992; von Ranson et al. 1992); alkylalkenals and acetylthioalkylalkenals (Robert et al. 2004); epoxyalkanals and epoxyalkenals (Buettner and Schieberle 2001a); allylalcohols and allylketones (Boerger et al. 2003); esters (Breidbach and Schieberle 2008); numerous mono- and bicyclic ring systems, among these macrocyclic substances (Kraft 1999; Kraft et al. 2000; Matsuda et al. 2004); and substituted pyrazines (Masuda and Mihara 1986; Mihara and Masuda 1988; Wagner et al 1999). Nevertheless, despite the comprehensive approaches, only a limited number of extraordinarily potent compounds have been characterized within a large range of investigated substances. Interestingly, in several cases well-known high-potency odorants were selected as the starting point of the respective considerations and were systematically varied. Thereby, it was predominantly discovered that any molecular modification of these already established compounds led to a decline with regard to odor potency. This was found to be true in the case of tr-4,5-epoxy-(*E*)-dec-2-enal and 2-ethyl-3,5-dimethylpyrazine and their corresponding homologous series, as well as for oct-1-en-3-one and non-1-en-3-one and several others (Wagner et al. 1999; Buettner and Schieberle 2001a).

Some volatile alkylated phenols, which originate from thermal degradation of phenolic acids or lignin (Fahmi et al. 2007) or derive from microbiological modifications of these substances (Hereszytn 1986; van Beek and Priest 2000), represent another compound group that shows consistently low odor thresholds in foods and other materials (cf. Table 1). Furthermore, certain individual odorants within this group have been described in several studies to have diverse sensory properties. Due to their obviously high odor potencies, the odor thresholds of alkylated phenols have been evaluated extensively (cf. Table 1). The published data vary over wide ranges and a correlation of structure and odor threshold has so far not been demonstrated. Thus, the influence of the substitution pattern of alkylated phenols on their odor thresholds is still unclear. The present study aims to close this gap by providing a systematic elucidation of the relationships between chemical structure and odor quality, as well as odor threshold, of homologous series of monoalkylated and isomeric di- and trimethylated phenols. Odor threshold determinations were performed in air utilizing state-of-the-art aroma analytical techniques such as gas chromatography/olfactometry (GC/O) and dilution assays to compensate for any matrix effects, allowing for comparison of obtained threshold data between substances. A comprehensive protocol was developed for describing the respective attributes, paying special attention to the linguistic dimension of the complex process of odor naming.

Materials and methods

Chemicals

The following reference compounds were used in the present investigation: (*E*)-dec-2-enal, phenol, 2-methylphenol, 3-methylphenol, 4-methylphenol, 2,3-dimethylphenol, 2,4-dimethylphenol, 2,5-dimethylphenol, 2,6-dimethylphenol, 3,4-dimethylphenol, 3,5-dimethylphenol, 2-*n*-propylphenol, 4-*n*-propylphenol, 4-isopropylphenol, 2,3,5-trimethylphenol, 2,3,6-trimethylphenol, 2,4,6-trimethylphenol, 3,4,5-trimethylphenol, 4-*n*-pentylphenol, toluene, *o*-xylene, *m*-xylene, *p*-xylene, 3-ethyltoluene (Sigma Aldrich), 2-ethylphenol, 3-ethylphenol, 4-ethylphenol (Riedel-de-Haen), 3-*n*-propylphenol, 2-isopropylphenol, 3-isopropylphenol, 4-*n*-butylphenol, 4-*n*-hexylphenol (ABCR), 2,4,5-trimethylphenol, 4-*n*-heptylphenol, 4-*n*-octylphenol, and 4-*n*-nonylphenol (Alfa Aesar).

Evaluation of odor qualities

The sensory panel consisted of 13 assessors (3 males and 10 females, aged 25–41 years). Aqueous solutions each containing the particular phenols at isointense concentrations (distinctly perceivable) were prepared. The solutions (20 mL) were filled in glass vessels (140 mL) and presented to the panel. The odor attributes of the phenols were determined according to the protocol described by Czerny et al. (2008) and summarized as follows.

In a first session, the panelists were asked to evaluate the odor qualities of the solutions based on their personal experience. Multiple descriptors for a compound were permitted. The sensory test was repeated a week later, and the frequency of attribute naming in both sessions was determined and expressed on an absolute percentage basis (percentage of panelists agreeing on a specific term). Due to the possibility of multiple attribute naming, percentages can reach 100% for one specific term but do not add up to 100% for all terms in total.

High-resolution GC/O

High-resolution GC/O (HRGC/O) analyses were performed with a type 5160 gas chromatograph (Carlo Erba). The analyses were accomplished using DB-FFAP, DB-1701, and DB-5

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Table 1 Occurrence and orthonasal odor thresholds of alkylated phenols

Odorant	Identified as odor-active compound in (selection)	Odor threshold (ranges)[a]
Phenol	Mushrooms[b]	31[c]–10 000[d]
3-Methylphenol	Espresso[e], wine[f], and rubber[g]	31[h]–800[i]
4-Methylphenol	Beef[j], cheese[k], cocoa[l], espresso[e], honey[m], piggery air[n], rubber[g], and soy milk[o]	2.7[p]–200[i]
3-Ethylphenol	Black tea[q], cocoa[l], and espresso[e]	1.7[h]–800[i]
4-Ethylphenol	Wine[f,r] and whiskey[s]	21[h]–600[i]
4-Vinylphenol	Rice[t] and wine[f]	10[u]–11[v]
3-*n*-Propylphenol	Cow shed air[w] and piggery air[w]	—
4-Allylphenol	Cherries[x]	—

[a] Odor threshold in µg/L water; the lowest and the highest values found in literature are listed.
[b] Lizarraga-Guerra et al. (1997).
[c] Young et al. (1996).
[d] Hoak (1957).
[e] Buettner and Griess (2004).
[f] Cullere et al. (2004).
[g] Breuer et al. (2002).
[h] Czerny et al. (2008).
[i] Dietz and Traud (1978).
[j] Kerscher and Grosch (1997).
[k] Kubickova and Grosch (1997).
[l] Frauendorfer and Schieberle (2006).
[m] Blank et al. (1989).
[n] Czerny et al. (2001).
[o] Lozano et al. (2007).
[p] Karagül-Yüceer et al. (2003).
[q] Schuh and Schieberle (2006).
[r] Lee and Noble (2003).
[s] Poisson and Schieberle (2008b).
[t] Jezussek (2002).
[u] Buttery et al. (1988).
[v] Pyysalo et al. (1977).
[w] Christlbauer (2006).
[x] Schmid and Grosch (1986).

capillaries (30 m × 0.32 mm, film thickness 0.25 µm, J & W Scientific). The helium carrier gas flow was set at 1.5 mL/min. The compounds eluting at the end of the capillaries were split with a Y-splitter (J & W Scientific; ratio 1:1 v/v) and transferred via 2 deactivated capillaries (0.5 m × 0.2 mm, J & W Scientific) to a flame ionization detector and a heated sniffing port (temperature: 250 °C). The samples were applied onto the capillaries using a cold-on-column injector at 40 °C. After 2 min, the oven was heated at a rate of 8 °C/min to 230 °C (DB-FFAP) and 250 °C (DB-1701 and DB-5), respectively, and held for 5 min. Linear retention indices were determined by HRGC using mixtures of individual odorants dissolved in dichloromethane together with a series of *n*-hydrocarbons (C_6–C_{26}) dissolved in *n*-pentane, according to van den Dool and Kratz (1963).

Determination of odor thresholds

Odor thresholds were determined in air following the procedure described by Ullrich and Grosch (1987) using (*E*)-dec-2-enal as an internal odor standard. (*E*)-dec-2-enal and the respective target compounds were dissolved in dichloromethane at known concentrations. The original solutions were diluted stepwise by a factor 1:2 (v/v); and all solutions were applied to HRGC/O until no odor was perceivable. Flavor dilution (FD) factors of the internal standard and odorant were calculated according to Grosch (2001). The odor threshold was calculated using the following equation:

$$\mathrm{OT}_{\mathrm{odorant}} = \frac{\mathrm{OT}_{\mathrm{STD}} \times \mathrm{C}_{\mathrm{odorant}} \times \mathrm{FD}_{\mathrm{STD}}}{\mathrm{C}_{\mathrm{STD}} \times \mathrm{FD}_{\mathrm{odorant}}}.$$

$\mathrm{OT}_{\mathrm{odorant}}$: odorant odor threshold in air.

$\mathrm{OT}_{\mathrm{STD}}$: odor threshold of the internal standard (*E*)-dec-2-enal in air (2.7 ng/L, according to Boelens and van Gemert 1986).

C_{odorant}: odorant concentration in the initial solution.

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Table 2 Odor qualities, linear retention indices, and supplementary information of alkylated phenols

No.	Compound	Odor qualities[a]	Retention index[b] on			MW	CAS-number
			DB-FFAP	DB-1701	DB-5		
1	Phenol	Ink-like	1986	1167	1107	94.11	108-95-2
	Monoalkylated phenols						
2	2-Methylphenol	Medicinal and ink-like	2000	1244	1077	108.14	95-48-7
3	3-Methylphenol	Leather-like and ink-like	2077	1270	1100	108.14	108-39-4
4	4-Methylphenol	Horse stable–like and fecal	2071	1269	1100	108.14	106-44-5
5	2-Ethylphenol	Fruity, sweet and ink-like	2059	1330	1160	122.16	90-00-6
6	3-Ethylphenol	Leather-like and ink-like	2169	1371	1195	122.16	620-17-7
7	4-Ethylphenol	Horse stable–like, fecal, and medicinal	2161	1369	1193	122.16	123-07-9
8	2-*n*-Propylphenol	Smoky, sweet, and smoked ham–like	2128	1415	1244	136.19	644-35-9
9	3-*n*-Propylphenol	Leather-like, ink-like, and medicinal	2250	1463	1285	136.19	621-27-2
10	4-*n*-Propylphenol	Sweet and medicinal	2250	1463	1285	136.19	645-56-7
11	2-Isopropylphenol	Ink-like and fruity	2111	1414	1301	136.19	88-69-7
12	3-Isopropylphenol	Ink-like and leather-like	2232	1418	1335	136.19	618-45-1
13	4-Isoproplyphenol	Rubber-like	2227	1419	1336	136.19	99-89-8
14	4-*n*-Butylphenol	Sweet and ink-like	2360	1571	1386	150.22	1638-22-8
15	4-*n*-Pentylphenol	Mushroom-like and metallic	2461	1678	1486	164.24	14938-35-3
16	4-*n*-Hexylphenol	Mushroom-like and metallic	2573	1784	1588	178.27	2446-69-7
17	4-*n*-Heptylphenol	Coal firelighter–like and mushroom-like	2679	1886	1778	192.30	1987-50-4
18	4-*n*-Octylphenol	Musty	2780	1994	1884	206.32	1806-26-4
19	4-*n*-Nonylphenol	n.d.	2900	2100	1989	220.35	104-40-5
	Dimethylated phenols						
20	2,3-Dimethylphenol	Ink-like, sweet, and leather-like	2137	1387	1200	122.16	526-75-0
21	2,4-Dimethylphenol	Ink-like	2079	1344	1172	122.16	105-67-9
22	2,5-Dimethylphenol	Sweet and ink-like	2066	1342	1174	122.16	95-87-4
23	2,6-Dimethylphenol	Medicinal and ink-like	1894	1300	1128	122.16	576-26-1
24	3,4-Dimethylphenol	Horse stable–like, fecal, and ink-like	2208	1406	1221	122.16	95-65-8
25	3,5-Dimethylphenol	Ink-like and sweet	2163	1369	1196	122.16	108-68-9
	Trimethylated phenols						
26	2,3,5-Trimethylphenol	Ink-like, medicinal, rubber-like, and sweet	2211	1483	1296	136.19	697-82-5
27	2,3,6-Trimethylphenol	Ink-like, tea-like, and medicinal	2028	1440	1344	136.19	2416-94-6
28	2,4,5-Trimethylphenol	Ink-like and sweet	2200	1472	1382	136.19	496-78-6
29	2,4,6-Trimethylphenol	Ink-like	1986	1400	1226	136.19	527-60-6
30	3,4,5-Trimethylphenol	Spicy, ink-like, and smoky	2356	1551	1346	136.19	527-54-8
	Methylbenzenes						
31	Methylbenzene (toluene)	n.d.	1040	825	762	92.14	108-88-3
32	1,2-Dimethybenzene (*o*-xylene)	n.d.	1159	952	890	106.17	95-47-6
33	1,3-Dimethylbenzene (*m*-xylene)	n.d.	1120	922	867	106.17	108-38-3

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Table 2 Continued

No.	Compound	Odor qualities[a]	Retention index[b] on			MW	CAS-number
			DB-FFAP	DB-1701	DB-5		
34	1,4-Dimethylbenzene (*p*-xylene)	n.d.	1114	922	868	106.17	106-42-3
35	3-Ethyltoluene	Turpentine-like	1200	1013	961	120.19	620-14-4

[a] Odor qualities were determined according to Czerny et al. (2008); n.d, odor quality not detectable. Attributes with an occurrence ≥25% are listed in descending order.

[b] Retention indices were determined according to van den Dool and Kratz (1963).

C_{STD}: internal standard concentration in the initial solution.
$FD_{odorant}$: FD factor of the odorant.
FD_{STD}: FD factor of the internal standard.

The individual threshold of a compound was determined by a male assessor (age 41 years; assessor A) experienced in GC/O and a female assessor (age 24 years; assessor B) with no prior GC-sniffing experiments. The combined threshold was calculated as geometric mean of the individual thresholds.

Results

Altogether, the odor qualities of phenol, 17 monoalkylated phenols, 6 dimethylated phenols, and 5 trimethylated phenols were investigated by the trained sensory panel during 2 sessions. Among the investigated compounds were methylated, ethylated, and *n*-propylated phenols substituted in ortho-, meta-, and para-position, with regard to the latter phenols also their corresponding isopropylphenols, as well as a homologous series of monoalkylated unbranched para-phenols (side chain length of alkyl substitution: C_1–C_9). Odor quality naming by the panelists was recorded with regard to the naming of a respective descriptor, whereby the total number of panelists was expressed in percentage of panel members who agreed on a specific term for a given compound. As repeated naming was allowed, the single percentage values do not add up to 100%.

In part 2 of the investigation, the odor detection thresholds of these compounds in air were determined by HRGC/O (Ullrich and Grosch 1987). In order to investigate the importance of the hydroxyl group for the flavor characteristics of alkylated phenols, toluene and xylene isomers, as well as 3-ethyltoluene, were included in the study. For providing an overview, the main odor descriptors and further supplementary chemomolecular data of the investigated phenols are summarized in Table 2.

A detailed discussion of the chemosensory properties of the investigated compounds is presented in the following:

Odor quality evaluations

Odor qualities of monoalkylated phenols

2-Alkylphenols. The odor character of 2-methylphenol was described by most panelists (60%) to be medicinal and ink-like (about 25 %) was reported as an additional attribute. Prolonging the alkyl chain to yield 2-ethylphenol, the aroma quality shifted dramatically to a preponderant fruity impression (close to 90%), accompanied by sweet and ink-like notes (35%). Further elongation erased the fruity note nearly completely, so that the smoky and smoked ham–like characters together with a sweet note were specified in 2-*n*-propylphenol (cf. Figure 1a). Still, only about 25–30% of the panelists agreed on each of the 3 attributes in each case, showing that the reported descriptors were not as unequivocally recorded as was the case for the fruity note in 2-ethylphenol. The medicinal note in 2-ethyl- and 2-*n*-propylphenol was just recorded by a minor panel proportion (around 20%).

3-Alkylphenols. The three 3-alkylphenols 3-methyl-, 3-ethyl, and 3-*n*-propylphenol were consistently characterized with the main attribute leather-like (40–50% of the panel members) followed by ink-like and medicinal notes as additional descriptors with panel naming values ranging between about 20% and 35% (cf. Figure 1b). There was no attribute that was agreed on by more than 50% of the panel members in all 3 cases.

4-Alkylphenols. The methylated and the ethylated phenol in para-position was characterized by both a horse stable–like as well as a fecal odor attribute. Whereas naming of these attributes amounted to about 90% for 4-methylphenol, the same notes were agreed upon to a lower extent (about 60%) for 4-ethylated phenol and were not cited at all for 4-*n*-propylphenol. Instead, there was a slight increase in naming of ink-like and medicinal notes and a number of other attributes that in neither case reached a higher agreement than 30%. According to this relative diversity, 4-*n*-propylphenol was described with medicinal and sweet as main attributes but still reaching only about 30% agreement in each case and additionally as being ink-like, fecal, and fruity. However, these terms were specified with even lower agreement (cf. Figure 1c). A common term exceeding 30% of agreement was not defined.

Comparison of n- and isopropylphenols. Comparing the odor descriptors of the *n*- and isopropylphenol isomers (Figure 1a–d), it first becomes evident that isomerization of the

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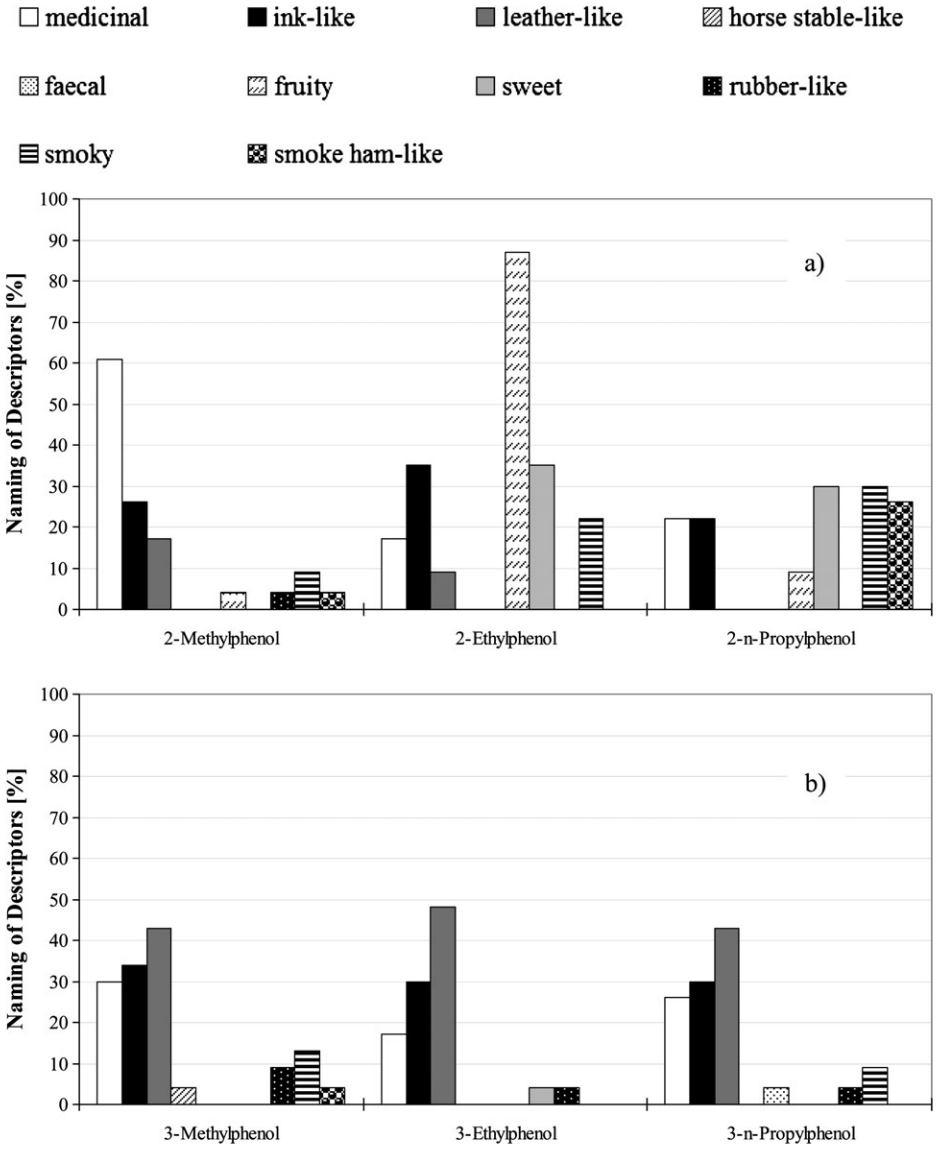

Figure 1 Continued

even-chained carbon group led to distinct changes in odor attribute naming in each case.

A shift in the naming of odor attributes in the 2-propylphenol isomers was observed from a relatively inconsistent description with sweet, smoky, and smoked ham–like notes (between 25% and 30% agreement of naming in each case in consecutive order of naming), the attribute naming changed to a relatively high consent for the iso-isomer with ink-like (60%) and fruity (40%) notes.

In the case of 4-propylphenol isomers, the same was true for the development of a relatively pronounced rubber-like note (about 45%) in the iso-form, whereas the even-chained compound represented medicinal and sweet notes.

By contrast, the same main attributes for the 3-propylphenol derivatives were named in each case (iso- and *n*-form): ink-like, leather-like, and medicinal. However, a slight shift in the agreement values was recorded with the leather-like attribute being preponderant and the medicinal descriptor being the least pronounced term in 3-*n*-propylphenol, whereas ink-like was the term most often agreed on in 3-isopropylphenol, followed by the 2 other terms leather-like and medicinal in consecutive order.

As para-substitution was found to be associated with an exceptionally high agreement regarding the odor quality naming, especially for the methylated phenol, prolongation of the unbranched carbon chain in this position was further investigated with regard to odor character development. As displayed in Figure 2, the originally pronounced fecal note decreased dramatically with increasing chain length, dropping from values of about 90% agreement to 60% (4-ethylphenol) and further to values being consistently below 10% for the remaining compounds. On the other hand, the medicinal note

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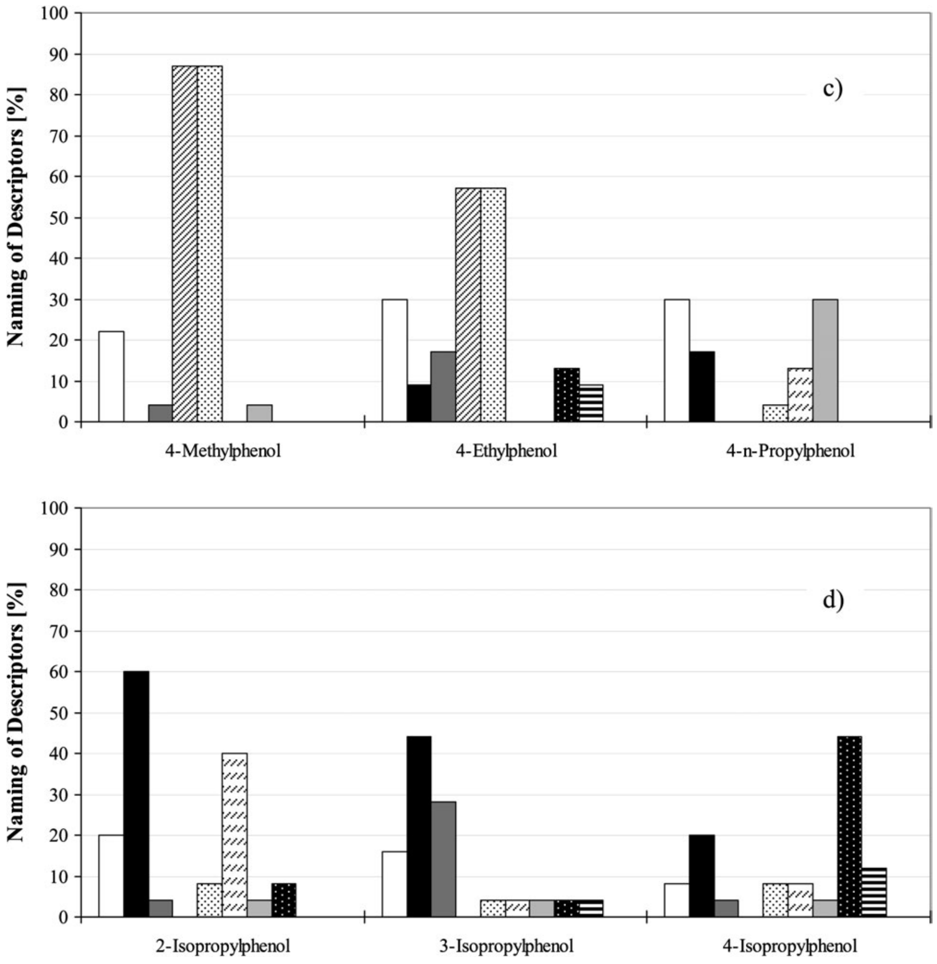

Figure 1 Distribution of odor attributes of monoalkylated **(a)** ortho-, **(b)** meta- and **(c)** para-phenol homologues, and **(d)** isopropylphenol isomers.

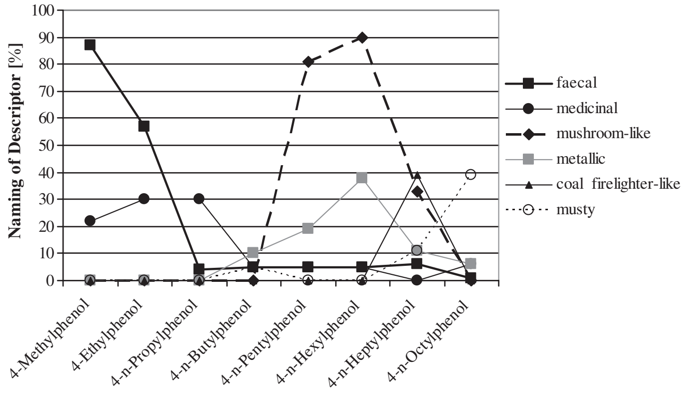

Figure 2 Distribution of odor attributes of unbranched monoalkylated para-phenols (C_1–C_8).

(about 20–30% in 4-methyl- and 4-ethylphenol) prevailed, thus becoming the main attribute in 4-*n*-propylphenol. With regard to 4-*n*-butylphenol, no major consent concerning a specific odor attribute could be reached, with all attributes being agreed upon by less than 30% of the panel members. Characters named, among others, were sweet and ink-like notes.

However, it is interesting to note that starting from the C_5-alkylated phenol, an intense mushroom-like odor note developed that was recorded for 4-*n*-pentyl- and 4-*n*-hexylphenol to be very clearly perceivable (80–90% agreement) and was described as being comparable to the characteristic smell of oct-1-en-3-one. Accordingly, the pentyl- and hexyl-derivatives were characterized to be predominantly mushroom-like in odor character, together with a metallic odor quality (an attribute that is interestingly also often recorded for oct-1-en-3-one). These attributes decreased in the case of the heptyl-derivative, which was described to have an additional coal firelighter–like smell (40% of panel agreement). 4-*n*-Octylphenol was described with musty odor attribute. Aqueous solutions of 4-*n*-nonylphenol at a concentration of 500 mg/L exhibited no odor, so that an attribute assignment could not be performed.

Odor qualities of di- and trialkylated phenols

With regard to the dimethylated phenols, a broad diversity of attributes was recorded with most compounds being

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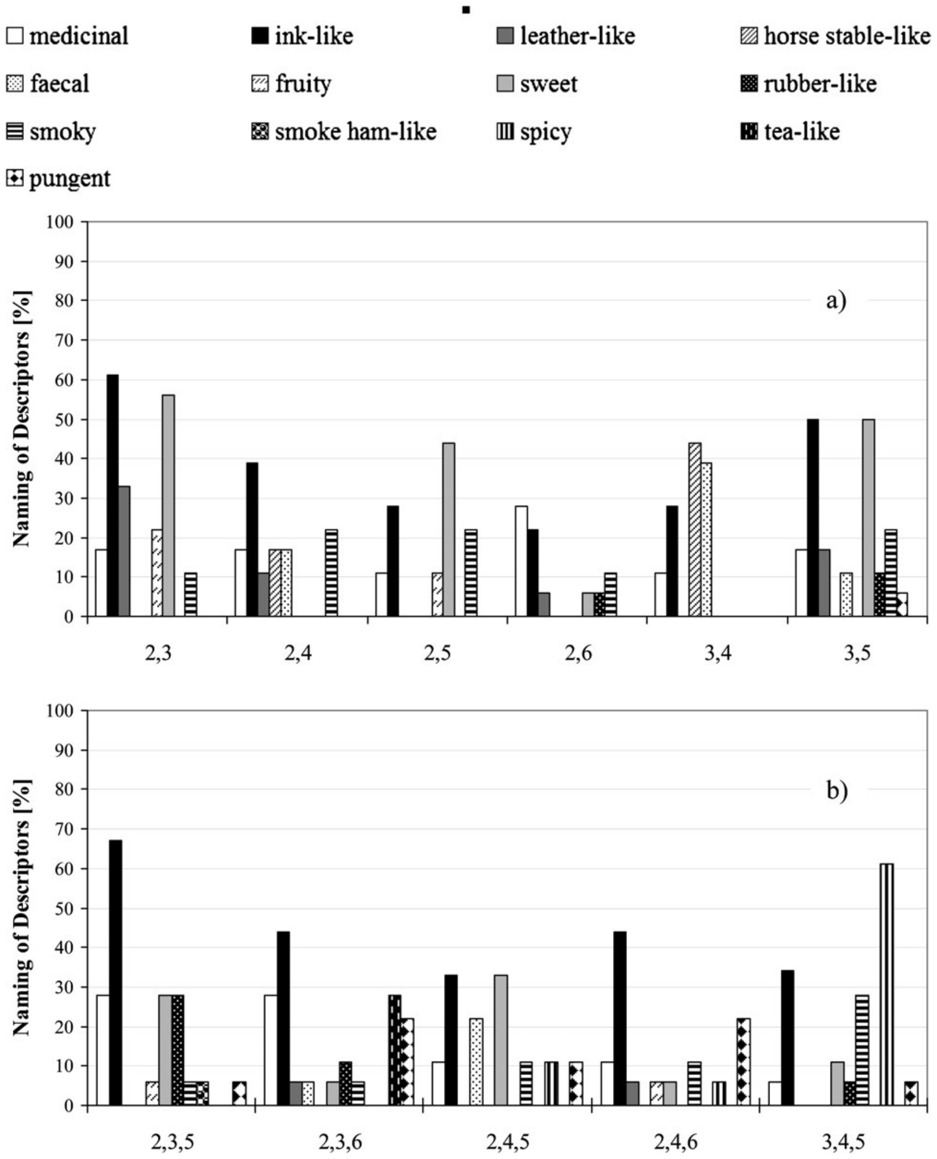

Figure 3 Distribution of odor attributes of **(a)** dimethyl- and **(b)** trimethyl phenols.

described by terms that reached consent values ≤50% and only 2,3-dimethylphenol being rated as ink-like and sweet by the majority of the panel. Generally, all 6 dimethylated phenols exhibited ink-like odor impressions. Ink-like was even reported for 2,3-, 2,4-, and 3,5-dimethylphenol as the dominant attribute (cf. Figure 3a). Specifically, panel consent reached up to 60% for 2,3-dimethylphenol and 50% for 3,5-dimethylphenol with regard to the ink-like odor attribute, whereas naming of this term was between just 20% and 40% for the remaining compounds. Apart from that, the medicinal odor attribute was the main descriptor of 2,6-dimethylphenol, and it was additionally named in several other cases (2,3-, 2,5-, and 3,5-dimethylphenol). The sweet attribute prevailed in 2,5-dimethylphenol and was also noted as an important term for 2,3-dimethylphenol and 3,5-dimethylphenol (as discussed above). Overall, the main exception with regard to the dominant odor attributes was 3,4-dimethylphenol, which showed predominantly horse stable–like and fecal odor notes (about 40% agreement in each case). Other additional attributes were smoky for all compounds with the exception of 3,4-dimethylphenol and leather-like with the exception of 2,5- and 3,4-dimethylphenol.

With regard to the 5 investigated trimethyl phenols, it was found that the components of this group were again characterized by a range of diverse descriptors with most of the named attributes not reaching a higher consent than 50% (cf. Figure 3b). The only exceptions were the ink-like attribute, which was reported by close to 70% of the panelists for 2,3,5-trimethylphenol, and a specific spicy odor note for

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Table 3 Odor detection thresholds of alkylated phenols in air (nanograms per liter air; nanomoles per liter in parenthesis) as determined by HRGC/O

	Substitution pattern[a, b]		
Substituent	Ortho (2-)	Meta (3-)	Para (4-)
Methyl	7.8 (0.072)	0.56 (0.0052)	0.12 (0.0011)
Ethyl	8.5 (0.0696)	0.052 (0.0004)	7.4 (0.0606)
n-Propyl	47 (0.345)	0.042 (0.0003)	7.4 (0.0543)
Isopropyl	22 (0.162)	0.10 (0.0007)	42 (0.308)
n-Butyl	n.d.	n.d.	126 (0.839)
n-Pentyl	n.d.	n.d.	180 (1.10)
n-Hexyl	n.d.	n.d.	124 (0.696)
n-Heptyl	n.d.	n.d.	93 (0.484)
n-Octyl	n.d.	n.d.	180 (0.872)
Dimethylated phenols			
2,3-Dimethylphenol	1.7 (0.014)		
2,4-Dimethylphenol	27 (0.221)		
2,5-Dimethylphenol	1.9 (0.016)		
2,6-Dimethylphenol	2.4 (0.020)		
3,4-Dimethylphenol	143 (1.17)		
3,5-Dimethylphenol	36 (0.295)		
Trimethylated phenols			
2,3,5-Trimethylphenol	88 (0.646)		
2,3,6-Tirmethylphenol	17 (0.125)		
2,4,5-Trimethylphenol	51 (0.375)		
2,4,6-Trimethylphenol	36 (0.264)		
3,4,5-Trimethylphenol	502 (3.69)		
Methylbenzenes			
Methylbenzene (toluene)	>1010		
1,2-Dimethybenzene (*o*-xylene)	>900		
1,3-Dimethylbenzene (*m*-xylene)	>1120		
1,4-Dimethylbenzene (*p*-xylene)	>1030		
3-Ethyltoluene	539 (4.48)		

Odor detection thresholds in air were determined according to Ullrich and Grosch (1987).
[a] N.d., not determined.
[b] The odor detection threshold of phenol was 48 ng/L air (0.511 nmol/L).

3,4,5-trimethylphenol that was also detected with low agreement in 2,4,5- and 2,4,6-trimethylphenol but was not recorded in any other of the investigated alkylated phenols. Interestingly, this attribute was described as spicy, exhibiting a resemblance to 3-hydroxy-3,5-dimethyl-2(5H)-furanone (sotolone).

Also for the investigated trimethyl phenols, the ink-like attribute was found to be a predominantly mentioned descriptor, dominating the odor profiles of 4 of the 5 compounds. The only exception was 3,4,5-trimethylphenol, which was characterized as being spicy with a lower agreement for ink-like as discussed above. Sweet, medicinal, leather-like, and pungent were named for all trimethyl phenols as additional attributes, whereas sweet was main descriptor together with ink-like in the case of 2,4,5-trimethylphenol. Interestingly, 2,3,6-trimethylphenol was characterized as the only

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Table 4 Individual and group odor detection thresholds of selected alkylated phenols (compounds are represented according to their degree of variation in decreasing order)

No.[a]	Compound	Odor detection threshold (ng/L air)			Variation[b]
		Panelist A	Panelist B	Group[c]	
7	4-Ethylphenol	2.6	21	7.4	8.1
5	2-Ethylphenol	3.0	24	8.5	8.0
9	3-*n*-Propylphenol	0.098	0.018	0.042	5.4
24	3,4-Dimethylphenol	330	62	143	5.3
25	3,5-Dimethylphenol	83	16	36	5.2
31	3,4,5-Trimethylphenol	1005	251	502	4.0
16	4-*n*-Hexylphenol	250	62	124	4.0
20	2,3-Dimethylphenol	2.6	1.1	1.7	2.4

[a] Numbering refers to Table 2.
[b] Variation of individual thresholds was calculated as a ratio of higher to lower threshold.
[c] The group odor threshold was calculated as a geometric mean of the individual thresholds of panelists A and B.

compound with a tea-like note as an important additional attribute, exhibiting a resemblance to black tea.

Odor detection threshold evaluations

Odor detection thresholds of monoalkylated phenols

The odor detection thresholds of each compound were evaluated by determining their odor threshold in air applying the HRGC/O method described by Ullrich and Grosch (1987) using (*E*)-dec-2-enal as an internal odor standard. This procedure offered the advantage that compounds that might be present as odor-active impurities in the reference compound (Czerny et al. 2008) are separated from the odorant during GC. In consequence, an influence of such components on the results is avoided. To display the resulting data for absolute comparison regardless of the respective molecular weights of the investigated compounds, the threshold data were additionally expressed on a molar basis (cf. Table 3).

The threshold data were obtained by 2 assessors via HRGC/O analyses, and the resulting odor thresholds are given as a mean of the individual thresholds. The highest threshold variations were found for the compounds listed in Table 4 in a range from a factor of 2.4–8.1. However, the variations in the individual thresholds of the remaining 22 phenols were a factor 2.0 or lower (data not shown). Due to the fact that the series of 1:2 (v/v) dilutions were analyzed during threshold determination, variation factors ≤2 can be assumed as the limits of error of this method.

To start with, the odor threshold of phenol was determined to be 48 ng/L air. Substitution of the phenol ring with a methyl group in position 2 decreased the threshold by a factor of 6 (7.8 ng/L for 2-methylphenol) (cf. Table 3). Elongation of the hydrocarbon chain resulted in no significant increase in odor activity. The threshold of 2-ethylphenol (8.5 ng/L) was comparable to 2-methylphenol, and the values of 2-*n*-propylphenol (47 ng/L) and 2-isopropylphenol (22 ng/L) were within the range of phenol.

In contrast to ortho-alkylphenols, a significant effect on the respective odor thresholds was observed by shifting the alkyl groups to the meta-position. In comparison to phenol, the thresholds of 3-methylphenol (0.56 ng/L), 3-ethylphenol (0.052 ng/L), 3-*n*-propylphenol (0.042 ng/L), and 3-isopropylphenol (0.10 ng/L) decreased by factors from 86 up to even 1140 and the compounds showed also lower thresholds than the corresponding para-alkylated phenols, except for 4-methylphenol.

4-Methylphenol, with an odor threshold of 0.12 ng/L air,was elucidated as an additional compound with a low odorthreshold. However, a prolongation of the alkyl group inthe series 4-ethylphenol, 4-*n*-propylphenol, and 4-isopropylphenol led to increases of the odor thresholds (7.4–42 ng/L), so that their values were comparable with ortho-alkylated phenols. Subsequent elongation of the hydrocarbon chain, resulting in the homologous series 4-*n*-butylphenol to 4-*n*-octylphenol, caused additional increases in the odor threshold values (93–180 ng/L). 4-*n*-Nonylphenol was the only investigated monoalkylphenol whose odor threshold can be regarded as very low, exceeding 1000 ng/L.

Influence of di- and trimethylation on odor detection thresholds

An additional methylation of 4-methylphenol in ortho- and para-position, respectively, increased the thresholds of 2,4-dimethylphenol (27 ng/L) and 3,4-dimethylphenol (143 ng/L) by factors of 225 and 1190, respectively.

However, a weak increase in odor threshold by a factor of 3–4 was detected when a methyl group was substituted to 3-methylphenol in position 2 (2,3-dimethylphenol, 1.7 ng/L) and 6 (2,5-dimethylphenol, 2.4 ng/L). In contrast, methyl substitution in positions 4 (3,4-dimethylphenol, 143 ng/L) and 5 (3,5-dimethylphenol, 36 ng/L) caused drastic increases in the odor thresholds. It can therefore be concluded that methyl substitution in the direct vicinity of the hydroxy group favors low odor thresholds.

Starting from 2-methylphenol, which has been identified as a medium-active compound (7.8 ng/L), methylation led to minor changes in odor threshold data. The threshold analyzed for 2,4-dimethylphenol was found to be a factor 3.5 higher compared with 2-methylphenol. The thresholds of the remaining phenols were slightly lower (1.7–2.4 ng/L).

Five of the 6 existing trimethyl phenols were investigated. The additional methyl substitution of dimethylphenols resulted in odor thresholds in a range of 17–502 ng/L (cf. Table 3), indicating that trimethyl phenols are characterized by lower odor thresholds than dimethylphenols.

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Influence of hydroxy function of phenols on odor quality and odor detection threshold data

Finally, the influence on odor character of the polar hydroxy group in phenol was studied. For this purpose, the odor qualities of selected compounds that differed from the phenol structure by replacement of the hydroxy by the apolar methyl group were determined. Starting with phenol, the replacement caused generally a strong decrease in odor detectability of the phenol counterpart toluene because it was not perceivable at a concentration of 1010 ng/L (cf. Table 3). The same result was obtained for all xylenes, whose threshold concentrations exceeded a set value of 900 ng/L. As example, *m*-xylene when compared with its analogue 3-methylphenol (0.56 ng/L) had a much higher odor threshold of at least a factor 2000. In contrast to this, 3-ethyltoluene exhibited a turpentine-like smell, but we detected an odor threshold for this compound (539 ng/L). Despite this, when compared with its analogue 3-ethylphenol (0.052 ng/L), the replacement of a hydroxy by a methyl group decreased odor threshold by a factor 10400 for this substance.

Discussion

The results clearly show that the odor detection thresholds and qualities of alkylated phenols depend significantly on the substitution pattern.

Alkyl substitution of phenol in position 3, as well as methylation in para-position, was found as an important factor causing low odor detection threshold values. All other investigated ortho- and para-alkylated phenols—with the exception of 4-methylphenol—as well as dimethyl- and trimethyl phenols exhibited higher odor threshold values in comparison to meta-alkylated phenols. Thus, these substitution patterns are disadvantageous with regard to this aspect.

Regarding odor quality, this investigation clearly demonstrates the complexity and general problem of odor quality determination:

On the one hand, there were some concise observations. Most specifically, meta-alkylated phenols were found to represent leather- and ink-like odor notes, as well as having a medicinal smell. However, there is little or no correlation of structure and odor quality of the remaining phenols investigated in this study.

One might be tempted to simply relate these observations to the increasing knowledge on the complexity of the physiological processes that are involved in flavor perception and interpretation. Starting from the periphery, there are a number of effects that might be the underlying principles causing the observations made within this study: metabolism effects prior to odorant receptor activation, the complex patterns of odor receptor activation itself, as well as the subsequent coding and processing steps in the olfactory bulb and further on into the higher regions of the central nervous system (Gottfried et al. 2006; Doucette and Restrepo 2008; Furudono et al. 2009; Schilling et al. 2010).

This complexity seems to be mirrored to some extent in the data provided here:

For example, attribute naming seemed to increase consistently in complexity in relation to an increase in structural complexity, as was observed for the dimethylated and trimethylated phenols. Therefore, one might assume that the more complex polyalkylated phenols might have triggered more complex patterns, for example, by activating more diverse receptor patterns, as such complexity together with pattern recognition has been shown to be an underlying principle in human odor chemosensation (Zou et al. 2001; Hasin et al. 2008). Interestingly, such agreement between combinatorial receptor code schemes has been demonstrated recently by comparing murine receptor codes with human odorant perception for 12 common natural phenol derivatives (Furudono et al. 2009). Despite carrying out these experiments across different species, there was clear evidence that odorants discriminated by murine receptor codes were also differently perceived by humans. It would be highly interesting to investigate this system with the extended molecular database at hand in this study. For these polysubstituted substances, agreement on specific terms was barely achieved with relatively low consistent odor naming values below 50%.

Still, it should be kept in mind that the descriptors represented within this study might be classified in related clusters. Such clustering has been attempted numerous times before and is hard to achieve. As an example, the horse stable–like and leather-like smells may be assumed to be related terms. However, when regarding the connective occurrence of naming the horse stable–like, fecal, and leather-like attributes, it becomes evident that the term "horse stable–like" defined by the panel was associated with the fecal notes of horse dung (explaining the congruent naming of both terms when regarding all investigated substances, cf. Figure 4) and not to the leathery saddle of horses, as may also be assumed. Accordingly, there was no congruent naming of the leather-like and horse stable–like attributes.

This example highlights one of the main problems of odor research, that is, not the quality perception per se but moreover the appropriate naming of the odor quality (Strube and Buettner 2010), an issue that is interestingly rarely addressed, even in the majority of structure–odor activity relationship investigations. To the authors' knowledge, such extensive odor quality determination studies have rarely been published in a similar manner as in the present paper. On the other hand, it might be that some odorants that do not have any biological "meaning" to panelists due to evolutionary or learning processes cannot be properly addressed simply due to a lack in vocabulary. Such effects are repeatedly observed in our group when investigators are dealing with "novel" smells, such as off-flavors that are artificial and unwanted by-products from manufacturing processes, for example, of plastics. Often, the smells occurring

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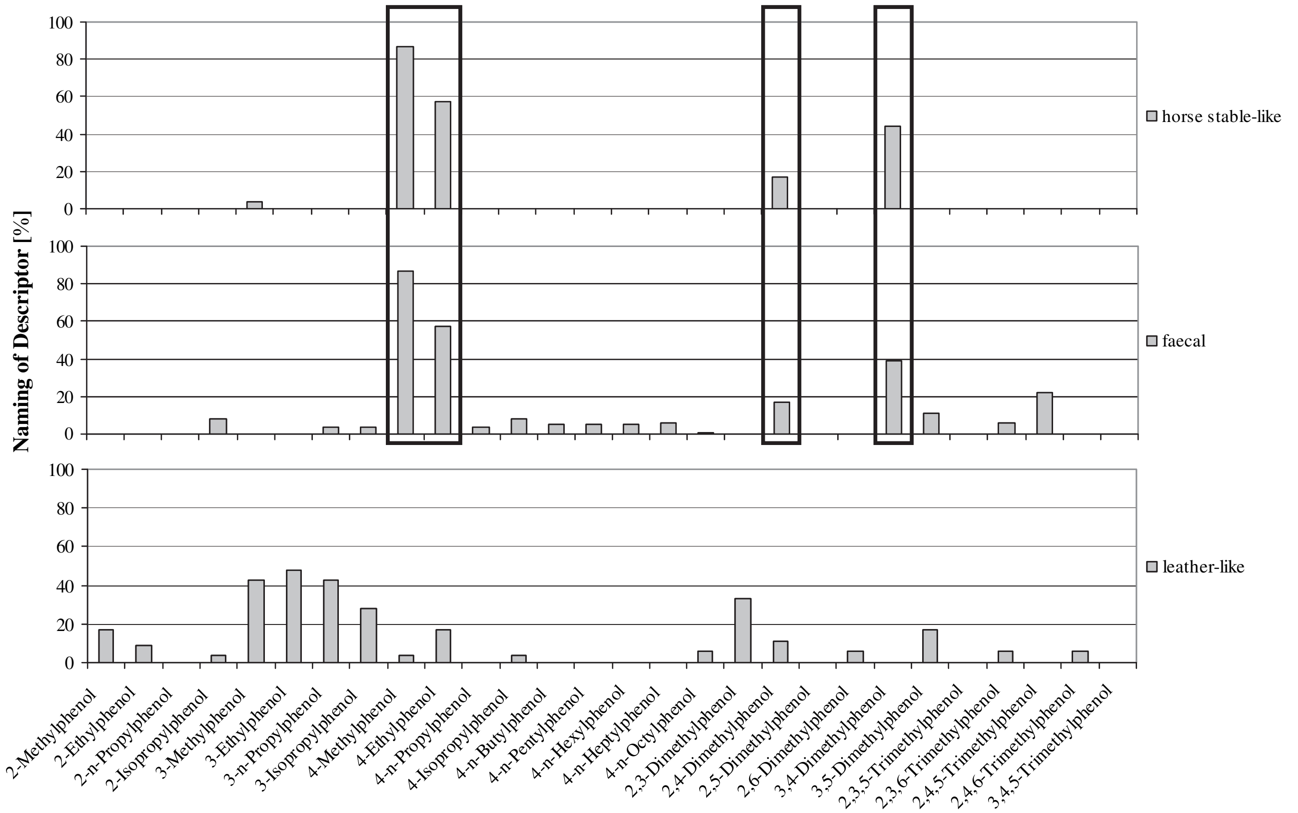

Figure 4 Relationships between the odor quality naming for the terms horse stable–like, fecal, and leather-like in all investigated alkylated phenols.

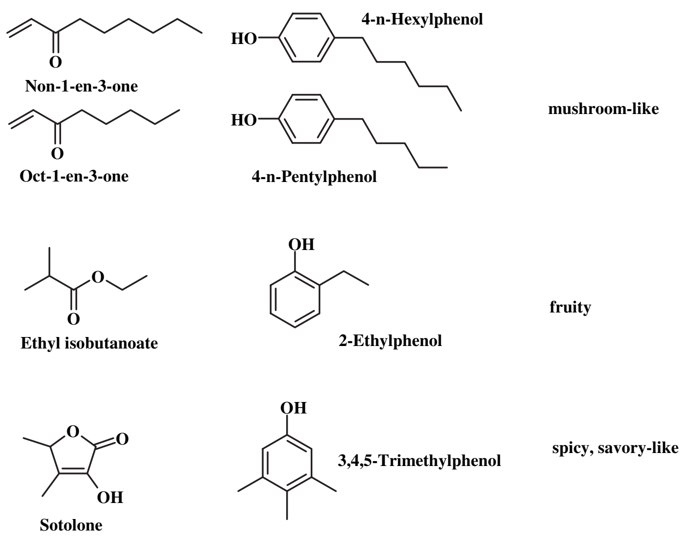

Figure 5 Other odorants exhibiting related odor qualities to specific alkylated phenols.

there can hardly be named as they have not been encountered before in any other context (Nuessli-Guth and Strube 2010).

With regard to specific and somehow unique odor descriptors, several interesting and surprising observations were made: For example, a mushroom-like odor with high resemblance to the specific smell of oct-1-en-3-one was predominant in 4-*n*-pentylphenol and 4-*n*-hexylphenol. To the authors' knowledge, only 4-*n*-pentylphenol has been previously identified as a food constituent, found in lovage (Bylaite et al. 2000). Moreover, neither of the aforementioned phenols have been described as odorants so far. Oct-1-en-3-one has often been described as a typical mushroom-like smelling odorant (Czerny et al. 2008) and has been elucidated as an aroma impact odorant of mushroom and in a series of other foods (Nijssen et al. 1996; Cho et al. 2006). Apart from this ketone, to our knowledge, only oct-1-en-3-ol, non-1en-3-one, and non-1-en-3-ol exhibit these specific mushroom-like odor qualities, which are very distinct. However, although oct-1-en-3-one and the phenols have the same common odor note, there is only little structural similarity of the compounds (cf. Figure 5). 4-*n*-Heptylphenol was also described as mushroom-like, but another attribute, resembling the smell of a coal firelighter, was dominant. An additional change in odor quality was detected for 4-*n*-octylphenol, which exhibited a musty odor.

Apart from that, a specific fruity note, with the typical smell of ethyl isobutanoate, was detected for 2-ethylphenol with a high frequency of naming and a characteristic spicy note similar to the smell of sotolone for 3,4,5-trimethylphenol. Again, when comparing the chemical structures, no clear structural relationship is evident (cf. Figure 5).

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It is also interesting to note that 2,4,6-trimethylphenol exhibited a mouldy odor, which is also a characteristic attribute of 2,4,6-trichloroanisole and 2,4,6-tribromoanisole (Spadone et al. 1990; Chatonnet et al. 2004). Accordingly, the arrangement of substituents in positions 2, 4, and 6 at the phenol ring might, in this case, be a prerequisite for a mouldy smell attribute due to the structural similarity of the methylated and halogenated compounds.

Odor threshold data in air have been reported in the literature for only some of the presently investigated phenols. The threshold values of phenol (47 ng/L), 4-methylphenol (0.14–1.0 ng/L), 2-*n*-propylphenol (44 ng/L), 3-*n*-propylphenol (0.098 ng/L), and 4-*n*-propylphenol (11 ng/L) (Leonardos et al. 1969; Blank et al. 1989; Christlbauer 2006; Czerny and Buettner 2009) were in accordance with the corresponding data analyzed in this study (cf. Table 1). However, the determined value of 4-ethylphenol (7.4 ng/L) was higher than reported by Christlbauer (2006) (0.46 ng/L).

Published threshold data in water by Dietz and Traud (1978) were not in accordance with some of the results presented in this study. The authors found only small differences in the odor activities of isomeric methylphenols (200–1400 μg/L) and ethylphenols (300–800 μg/L).

Generally, the odor thresholds of the meta-alkylated phenols were comparable with some other potent odorants, for example, (*E*,*E*)-deca-2,4-dienal (0.080 ng/L) (Gasser and Grosch 1990), (*E*)-non-2-enal (0.13 ng/L) (Schieberle and Grosch 1991), and 3-(methylthio)-propanal (0.14 ng/L) (Blank et al. 1989), which have been identified as important contributors to the aroma of various foods. Therefore, the odor activities of these alkylphenols can be appraised as being high.

It is interesting to note that the individual thresholds differed in most cases only marginally despite one assessor being experienced in HRGC/O (assessor A) and the other performing the sniffing analysis for the first time (assessor B). The result of this investigation indicates that the odor sensitivity of individual panelists might, at least for the substances under investigation here, not depend on experience. Still, it is clear that with regard to the threshold data, a wider panel data collection would be required. Nevertheless, the approach chosen in this study is highly time consuming, thereby providing precise data that are not biased by any matrix effects or subjected to contamination problems. Accordingly, this approach was preferred over a more general test on a larger panel scale. Further studies must be performed to elucidate panel variation in more detail.

Summarizing the data of the present study, one can conclude that with regard to odor quality, a number of interesting and also unexpected observations were made that cannot be explained on a simple structure–odor quality correlation basis. One might assume that with regard to odor quality characterization, the alkylated phenols do not only exhibit a broad diversity of characters among panelists but that also odor naming is a major issue in this context. Still, these studies highlight a path to further elucidate the complex phenomena behind odor characteristics and expression of what is perceived, most specifically with regard to substances that have not been addressed before and might be quite specific with regard to their occurrence in our everyday environment.

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