Chem. Senses 30: 755–760, 2005

doi:10.1093/chemse/bji067
Advance Access publication October 12, 2005

Olfactory Discrimination Ability for Aliphatic C6 Alcohols as a Function of Presence, Position, and Configuration of a Double Bond

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Abstract

The ability of human subjects to distinguish between aliphatic C6 alcohols differing in presence, position, or configuration (i.e., *cis–trans* geometry) of a double bond was tested. In a forced-choice triangular test procedure, 20 subjects were repeatedly presented with all 21 binary combinations of the seven stimuli and asked to identify the bottle containing the odd stimulus. I found (a) that as a group, the subjects performed significantly above chance level in all tasks but two and thus were clearly able to discriminate between most of the odor pairs presented; (b) marked interindividual differences in discrimination performance, ranging from subjects who were able to significantly distinguish between all 21 odor pairs to subjects who failed to do so with 10 of the tasks; (c) that odor pairs involving two hexenols were significantly more difficult to discriminate than odor pairs that involved hexanol and one of the hexenols; (d) that odor pairs involving hexenols sharing the same geometry but differing in the position of the double bond by only one carbon atom were significantly more difficult to distinguish than odor pairs that involved hexenols differing by two carbon atoms; (e) that odor pairs involving 4-hexenols were significantly easier to discriminate than 3-hexenols, which, in turn, were significantly easier to distinguish than 2-hexenols; and (f) that odor pairs involving two *cis*-hexenols were significantly more difficult to discriminate than odor pairs that involved two *trans*-hexenols. These findings demonstrate that the presence as well as the position and configuration of a double bond affected discriminability in a systematic manner and suggest that these molecular structural features may be important determinants of the interaction between stimulus molecule and olfactory receptor and thus may affect odor quality of aliphatic alcohols.

Key words: aliphatic alcohols, discrimination ability, double bond, humans, odor structure–activity relationships, olfaction

Introduction

Molecular structural features such as carbon chain length or nature and disposition of functional groups have been shown to play a crucial role in the interaction occurring between odor stimulus and olfactory receptor (Kaluza and Breer, 2000; Touhara, 2002). These molecular properties are then encoded as patterns of activation in the glomerular layer of the olfactory bulb (Johnson and Leon, 2000; Takahashi *et al.*, 2004; Johnson *et al.*, 2005), and it is now commonly agreed that these odorant-specific maps are critical for odor quality recognition and discrimination (Leon and Johnson, 2003; Xu *et al.*, 2003).

Psychophysical studies have demonstrated regular connections between carbon chain length of aliphatic odorants and odor quality as perceived by humans (Laska and Teubner, 1999; Laska and Hübener, 2001) and nonhuman species (Laska and Teubner, 1998; Laska *et al.*, 1999a,b). Similarly, the nature and disposition of functional groups appear to correlate with odor quality when tested using discrimination paradigms (Laska *et al.*, 2000; Laska, 2002).

Surprisingly, few psychophysical studies, in contrast, have so far assessed the impact of presence, position, and configuration (i.e., *cis–trans* geometry) of a double bond on odor quality perception (Bedoukian, 1971; Sakoda *et al.*, 1995), although these molecular structural features are also likely to affect the interaction between odorant and receptor. This assumption is supported by optical-imaging studies reporting small but characteristic changes in odor maps as a function of saturation (Uchida *et al.*, 2000; Ho *et al.*, 2005) and by psychophysical findings that showed presence, position, and configuration of a double bond to have a marked influence on the detection thresholds of esters (Takeoka *et al.*, 1998), alcohols (Hatanaka *et al.*, 1992), and aldehydes (Meijboom and Jongenotter, 1981).

Most of the psychophysical studies reporting qualitative differences between odorants differing in double-bond–related

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molecular features employed odor-profiling (Bedoukian, 1971; Anselmi *et al.*, 2000) or -scaling procedures (Hatanaka *et al.*, 1992; Sakoda *et al.*, 1995) that are presumed to be susceptible to cognitive influences (Corwin, 1992). To the best of my knowledge, no study so far has directly tested the discriminability of unsaturated aliphatic odorants, although this method largely avoids the disadvantages of poor resolution and semantic ambiguity (Wise *et al.*, 2000).

It was therefore the aim of the present study to provide first data on the olfactory discrimination ability of human subjects for unsaturated aliphatic odorants and to assess whether presence, position, and configuration of a double bond affect discrimination ability in a systematic manner. The rationale for choosing aliphatic C6 alcohols (hexanol and hexenols) as stimuli was that both threshold data (Hatanaka *et al.*, 1992) as well as qualitative descriptions (Bedoukian, 1971) for these compounds are at hand. Furthermore, these odorants include typical "green" odors (such as *cis*-3-hexen-1-ol and *trans*-3-hexen-1-ol, which are sometimes also referred to as "leaf alcohols") and thus are presumed to have some real-life relevance.

Materials and methods

Human subjects

A total of 20 healthy, unpaid volunteers (15 females and 5 males), 23–33 years of age, participated in the study. All were nonsmokers, and none had any history of olfactory dysfunction. All subjects had previously served in olfactory tests and were familiar with the basic test procedure. They were informed as to the aim of the experiment and provided written consent. The study was performed in accordance with the Declaration of Helsinki/Hong Kong.

Odorants

A set of seven odorants were used (Table 1). The rationale for choosing these substances was to test the discriminability of aliphatic odorants belonging to the same chemical class and differing only in the presence/absence, position, or configuration of a double bond (Figure 1). All substances were obtained from Sigma-Aldrich (Taufkirchen, Germany) and had a nominal purity of at least 99%. They were diluted using diethyl phthalate (Merck; Darmstadt, Germany) as the solvent. In an attempt to ensure that the odorants were of approximately equal strength when presented in squeeze bottles, intensity matching was performed by a panel of six subjects using an 8.7-g/l solution of iso-amyl acetate as the reference and adopting a psychophysical procedure similar to the one described by the American Society for Testing and Materials (ASTM, 1975).

Table 1 Substances and concentrations used

No.	Substance	Concentration (g/l)
1	1-Hexanol	2.7
2	*cis*-2-Hexen-1-ol	28.2
3	*cis*-3-Hexen-1-ol	84.6
4	*cis*-4-Hexen-1-ol	85.7
5	*trans*-2-Hexen-1-ol	28.3
6	*trans*-3-Hexen-1-ol	27.2
7	*trans*-4-Hexen-1-ol	28.4

Test procedure

A 40-ml aliquot of each odorant was presented in a 250-ml polyethylene squeeze bottle equipped with a flip-up spout. Subjects were instructed the manner of sampling and at the start of the first session were allowed time to familiarize themselves with the bottles and the sampling technique. Care was taken that the spout was only a short distance (1–2 cm) from the nasal septum during sampling of an odorant in order to allow the stimulus to enter both nostrils.

In a forced-choice triangular test procedure, 20 subjects were asked to compare three bottles and identify the one containing the odd stimulus. Additionally, after each decision, subjects were asked whether their choice was predominantly based on perceived differences in odor quality or on perceived differences in odor intensity. Each bottle could be sampled twice with an interstimulus interval of at least 10 s. Sampling duration was restricted to 1 s per presentation in order to minimize adaptation effects. The sequence of presenting the stimulus pairs was systematically varied between sessions and individual subjects while taking care that the presentation of a given odorant as odd or even stimulus was balanced within and between sessions. In order to control for possible cross-adaptation effects, the order in which the stimuli of a given triad was sampled was systematically varied between sessions. Approximately 30 s was allowed

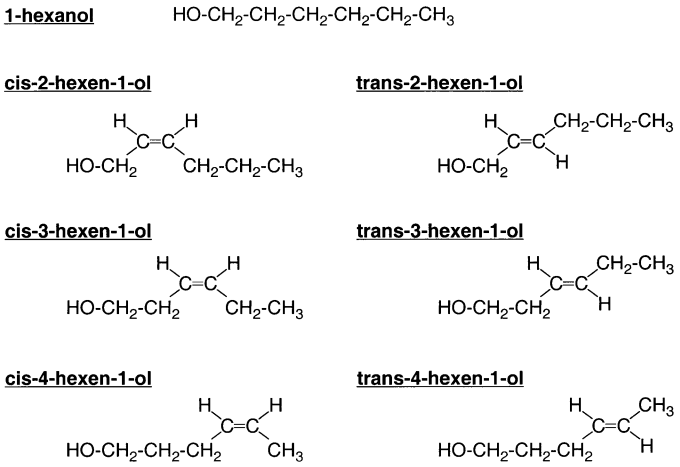

Figure 1 Chemical structure of the seven odor stimuli.

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between trials, and no feedback regarding the correctness of the subjects' choice was given.

Twenty-one different stimulus pairs were presented once per session, and testing was repeated in nine more sessions, each 1–3 days apart, enabling 10 judgements per stimulus pair and panelist to be collected.

Data analysis

The criterion for an individual subject to be regarded as capable of discriminating a given odor pair was set at 7 or more out of 10 correct decisions (two-tailed binomial test, $P < 0.05$). Accordingly, the criterion for the group of subjects to be regarded as capable of discriminating a given odor pair was set at 13 or more out of 20 subjects performing significantly above chance (two-tailed binomial test, $P < 0.01$).

Comparisons of group performance across tasks were made using the Friedman two-way analysis of variance (ANOVA). When ANOVA detected differences between tasks, this was then followed by pairwise Wilcoxon signed-rank tests for related samples to evaluate which tasks were responsible. Correlations between discrimination performance and structural similarity of odorants in terms of differences in position of a double bond were evaluated using the Spearman rank correlation coefficient and tested for significance by computing t values. Frequencies in discrete categories were compared using the chi-square test. All data are reported as mean ± SD.

Results

Figure 2 summarizes the mean performance of 20 subjects in discriminating between the 21 odor pairs. As a group, the human subjects performed significantly above chance level in all tasks but two (2–5 and 3–6, i.e., *cis*-2-hexen-1-ol vs. *trans*-2-hexen-1-ol and *cis*-3-hexen-1-ol vs. *trans*-3-hexen-1-ol) and thus were clearly able to discriminate between most of the odor pairs presented.

Interindividual variability was high, particularly in odor pairs that presented some difficulties to the subjects (see SDs in Figure 2). However, ANOVA detected significant differences in the group's performance between tasks (Friedman, $P < 0.001$), and subsequent pairwise tests revealed that the two tasks that were not discriminated above chance at the group level (2–5 and 3–6) were significantly more difficult than all other tasks (Wilcoxon, $P < 0.01$).

Figure 3 compares the mean discrimination performance of the 20 subjects with several subgroups of the 21 tasks. Odor pairs that involved two hexenols (Figure 3, bar A) were significantly more difficult to discriminate than odor pairs that involved hexanol and one of the hexenols (Figure 3, bar B) (Wilcoxon, $P < 0.01$).

Odor pairs that involved two *cis*-hexenols (Figure 3, bar C) were significantly more difficult to discriminate than odor pairs that involved two *trans*-hexenols (Figure 3, bar D) (Wilcoxon, $P < 0.01$).

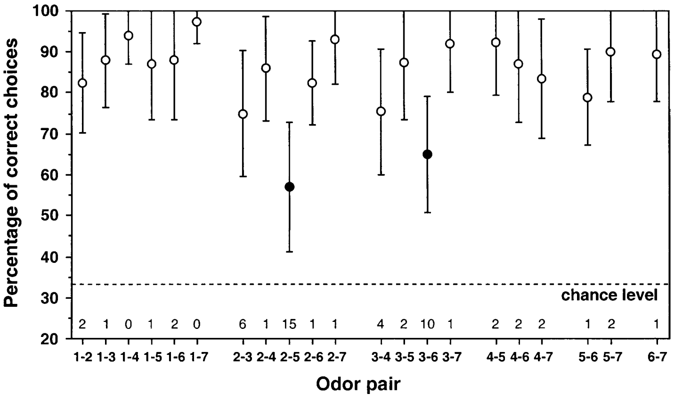

Figure 2 Performance of 20 subjects in discriminating between aliphatic C6 alcohols. Each data point represents the percentage (mean ± SD) of correct choices from 10 decisions per odor pair and subject. Filled symbols indicate odor pairs that were not discriminated above chance at the group level. The figures above the abscissa indicate the number of subjects that failed to perform above chance in the corresponding task. Names of substances are given in Table 1.

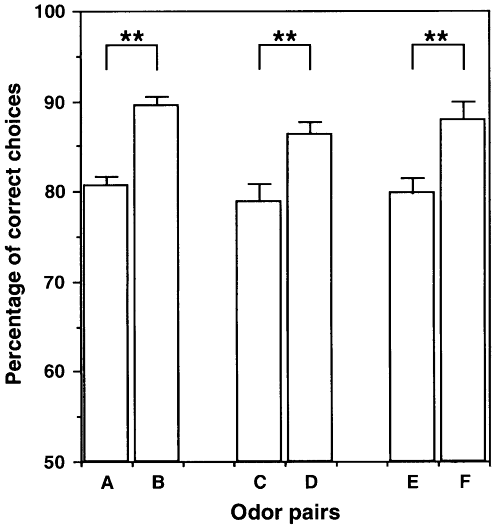

Figure 3 Performance of 20 subjects in discriminating between aliphatic C6 alcohols, averaged across subgroups of odor pairs. Each bar represents the percentage (mean ± SE) of correct choices from 10 decisions per odor pair and subject. A: odor pairs that involved two hexenols; B: odor pairs that involved hexanol and one of the hexenols; C: odor pairs that involved two *cis*-hexenols; D: odor pairs that involved two *trans*-hexenols; E: odor pairs that involved hexenols sharing the same geometry but differing in the position of the double bond by only one carbon atom; and F: odor pairs that involved hexenols sharing the same geometry but differing in the position of the double bond by two carbon atoms. $^{**}P < 0.01$.

Odor pairs that involved hexenols sharing the same geometry but differing in the position of the double bond by only one carbon atom (Figure 3, bar E) were significantly more difficult to discriminate than odor pairs that involved hexenols differing by two carbon atoms (Figure 3, bar F) (Wilcoxon, $P < 0.01$).

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Figure 4 illustrates the discriminability of the individual odorants. The frequencies at which a given odorant was involved when subjects failed to significantly discriminate an odor pair (Figure 4, lower part) ranged from only 6 such cases with odor 1 (1-hexanol) to 26 cases with odor 2 (*cis*-2-hexen-1-ol) and thus differed significantly between stimuli (chi square, $P < 0.05$). Likewise, the mean scores across the six tasks that involved a given odorant (Figure 4, upper part) differed significantly between stimuli (Friedman, $P < 0.001$), and subsequent pairwise tests showed odors 1 (1-hexanol), 4 (*cis*-4-hexen-1-ol), and 7 (*trans*-4-hexen-1-ol) to be significantly easier to distinguish from the other alcohols compared to the other members of the set of stimuli (Wilcoxon, $P < 0.05$ for all pairs).

Interindividual differences in subjects' ability to discriminate between the 21 odor pairs were quite large. The percentage of errors ranged from only 8% to 30%. Accordingly, the best panelist (interestingly not the panelist with the lowest percentage of errors) was able to significantly distinguish all 21 odor pairs, whereas the poorest performing subject failed to do so with 10 of the 21 tasks (see Figure 5).

Mean performance of the group of 20 subjects across the 10 test sessions was quite stable. Error rates did not differ significantly between sessions (Friedman, $P > 0.05$), and thus no learning or training effects at the group level were found.

With all 21 odor pairs, less than 10% of the decisions were reported to be based on perceived differences in odor intensity rather than odor quality.

Discussion

The results of this study demonstrate (a) that human subjects possess a well-developed olfactory discrimination ability for aliphatic C6 alkenols and (b) that presence, position, and configuration of a double bond affected discriminability in a systematic manner.

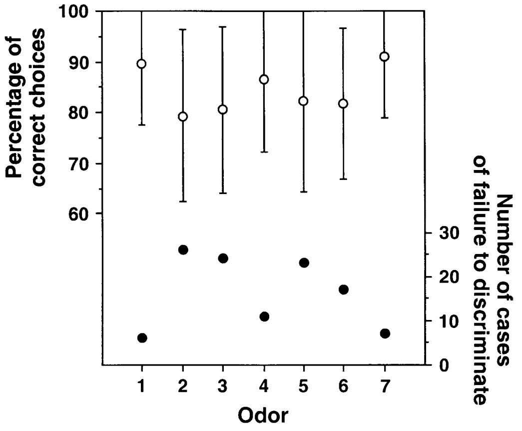

Figure 4 Discriminability of the seven aliphatic C6 alcohols. Open symbols represent the percentage (mean ± SD) of correct choices across the six tasks that involved a given odorant. Filled symbols indicate the number of cases in which a given odorant was involved when an odor pair was not significantly discriminated by a subject. Names of substances are given in Table 1.

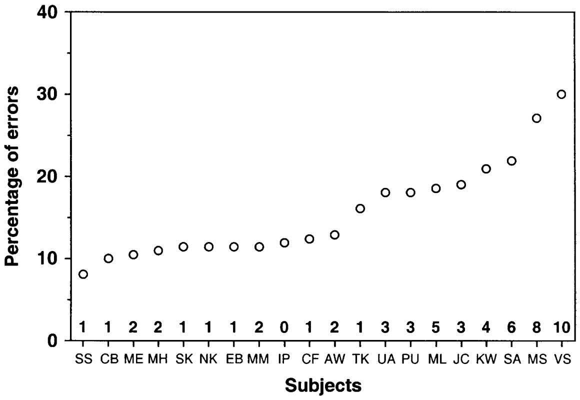

Figure 5 Distribution of individual performance in discriminating between the 21 odor pairs. Each data point represents the percentage of errors from 210 decisions per subject. The figures above the abscissa indicate the number of odor pairs that a subject failed to discriminate significantly above chance.

These findings lend support to the notions that the human sense of smell may be far better than the traditional view purports (Shepherd, 2004) and that it is capable of discriminating between almost any pair of odorants (Cain, 1995). However, the question arises whether the performance of the human subjects shown in the present study was indeed based on the ability of the olfactory system to discern between odor qualities or whether other sensory systems or other talents of the olfactory system may have been involved.

The trigeminal-stimulating properties found with the majority of odorants at high concentrations (Doty and Cometto-Muniz, 2003) raise the possibility that the nasal trigeminal system might have contributed to the discrimination performance. However, nasal pungency thresholds of human subjects for aliphatic substances, mediated by the trigeminal nerve, have been shown to be at least two and generally about four orders of magnitude higher compared to odor thresholds mediated by the olfactory nerve (Cometto-Muniz and Cain, 1995). Thus, the possibility of trigeminal involvement in the discrimination of odorants can be excluded.

Although the possibility that differences in perceived odor intensity might have contributed to the discrimination performance cannot be ruled out completely, this seems quite unlikely as the attempt to present stimuli at equal subjective intensities was confirmed by the fact that during the critical discrimination tasks more than 90% of the subjects' decisions were reported to be based on perceived differences in odor quality rather than odor intensity (see Test Procedure). Further, the few instances in which perceived differences in odor intensity were reported seem to mirror a subject's difficulty to discriminate at all as error rates in such cases tended to be higher compared to the regular case of reported differences in odor quality. Therefore, it seems reasonable to assume that the discrimination scores found here indeed reflect the ability of the human olfactory system to distinguish between odor qualities.

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The finding that odor pairs involving two hexenols were significantly more difficult to discriminate than odor pairs that involved hexanol and one of the hexenols (see Figure 3) demonstrates that the presence or absence of a double bond had a marked influence on the odor quality of the C6 alcohols. This should not be surprising given that the presence of a double bond prevents the free rotation of the molecule between carbon atoms and thus reduces its flexibility (Ohloff, 1994) which, in turn, is presumed to affect the options of interaction with an olfactory receptor (Sicard, 2002).

Psychophysical studies using odor-profiling methods also showed that the introduction of a double bond markedly changed odor quality. Anselmi *et al.* (2000) reported that unsaturated cyclic hydrocarbons have a "fruity" or "floral" character, whereas the corresponding saturated molecules lack these qualities and are described as "difficult to define." Similarly, Sakoda *et al.* (1995) reported that aliphatic nonenols clearly differ in their odor profiles from nonanol. In line with these findings, optical-imaging studies also reported that the presence of a double bond in hydrocarbons (Ho *et al.*, 2005) and C6 alcohols (Uchida *et al.*, 2000) led to small but characteristic changes in odor maps when compared to the glomerular activation patterns evoked by the corresponding saturated odorants.

The finding that odor pairs that involved hexenols sharing the same geometry but differing in the position of the double bond by only one carbon atom were significantly more difficult to discriminate than odor pairs that involved hexenols differing by two carbon atoms demonstrates that the position of a double bond affected odor quality of the C6 alcohols in a systematic manner (see Figure 3). This is in agreement with reports of regular changes in odor quality with shifting of the double bond of hexenols from position 2, which are described as "fruity" and "sweet," to position 4, which are described as "oily-fatty" and "herbal," with 3-hexenols taking an intermediate position between these qualitative descriptors (Hatanaka *et al.*, 1992). Using the same odor-profiling method, Sakoda *et al.* (1995) also found odor quality of nonenols to change systematically as a function of this molecular structural feature. The position of a double bond is believed to affect flexibility as well as overall shape and charges of a molecule (Ohloff, 1994), all features known to play a role in the interaction between odorant and receptor (Sicard, 2002).

Similarly, the finding that *cis*- versus *trans*-4-hexenol (odor pair 4–7) was significantly easier to discriminate than *cis*- versus *trans*-3-hexenol (odor pair 3–6), which, in turn, was significantly easier to distinguish than *cis*- versus *trans*-2-hexenol (odor pair 2–5, see Figure 2), indicates a regular connection between double-bond position and odor quality. The position of a double bond relative to an oxygen-containing and thus polar functional (alcohol) group is thought to systematically affect hydrophobicity of a molecule (Ohloff, 1994) and thus is believed to influence the affinity between ligand and receptor (Sicard, 2002). To the best of my knowledge, no optical-imaging study so far has systematically assessed whether shifts in double-bond position along a straight-chained carbon backbone leads to corresponding gradual changes in the glomerular representation of odorants.

Finally, the finding that odor pairs that involved two *cis*-hexenols were significantly more difficult to discriminate than odor pairs that involved two *trans*-hexenols (see Figure 3) demonstrates that configuration or geometry also had a marked influence on odor quality of the C6 alcohols. This is in contrast to studies that reported odor quality profiles of hexenols sharing the same position but differing in geometry to be very similar to each other (Hatanaka *et al.*, 1992) and that the geometries of nonenols had only little effect on odor quality (Sakoda *et al.*, 1995). It is interesting to note that detection thresholds for hexenols sharing the same position of the double bond but differing in geometry did not differ as a function of geometry (Hatanaka *et al.*, 1992), suggesting that the finding of the present study was not simply due to differences in perceptibility of the odorants. The configuration of a double bond, that is, *cis–trans* geometry, is known to affect the overall shape of a molecule (Ohloff, 1994), one of the structural features shown to be important in the olfactory primary process (Sicard, 2002).

Taken together, the findings of the present study provide evidence of a well-developed discrimination ability of human subjects for aliphatic C6 alkenols and evidence that presence, position, and configuration of a double bond affected discriminability in a systematic manner. This suggests that these molecular structural features may be important determinants of the interaction between stimulus and olfactory receptor and thus may be molecular properties affecting odor quality of aliphatic alcohols.

Further, the results suggest that testing the discrimination ability for structurally related substances may offer an efficient way to measure differences in odor quality with high resolution and a minimum of subjectivity and context dependence. Following this line of research may lead to archivally useful data upon which one could build a stable psychological space for odor quality.

Acknowledgements

I thank my panelists for their willingness to participate in this study and the Deutsche Forschungsgemeinschaft for financial support (La 635/10-2).

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Accepted September 20, 2005

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