Similarity of odor qualities and similarity of molecules ~ Examples of molecules that contain a *cis*-type carbon-carbon double bond or a thioether moiety ~

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Abstract The similarity of odor qualities by substituting the *cis*-type carbon-carbon double bond (*cis* -C=C-) for a thioether moiety (-S-) has been reported in some published papers. However, the degrees of the odor similarities were not reported. One of the objectives of this study is to measure the odor similarities by substituting the *cis* -C=C- for-S-. Another purpose of this study is to investigate the molecular features that contribute to the odor similarity in such cases. We employed the following two methods: 1) olfactory evaluations to measure the actual odor perception of the participants, and 2) computer chemistry to calculate the molecular features of the odorous compounds. As a result, it was confirmed that the odor quality did not significantly change in some cases though it was not a general trend when the *cis* -C=C- moiety was substituted for -S-. Similarities in the odors were mainly explained by the similarities in both the structural and electrostatic features based on the computational calculations. When the structural and electronic features were similar in two compounds, they are expected to produce similar odors.

Introduction

Several participants chose the same odor descriptor, "onion-like", for thiophene and cyclohexene (Figure 1-[a]) in our pilot olfactory evaluation tests. The selection of the same odor descriptor seemed rather peculiar, since thiophene contains a sulfur atom, while cyclohexene consists of only carbon and hydrogen atoms. To this issue, affirmative descriptions were found in previous reports (Boelens and Heydel, 1973, Boelens and van Germert 1993). They reported that the odor-character does not significantly change even if one substitutes a *cis* carbon-carbon double bond (*cis* -C=C-) for a sulfur atom (-S-) within odorous molecules (Figure 1-[b]).

However, the subjective degree of the odor similarity or the detailed descriptions of the odor qualities were not reported. Therefore, we tried to measure the degree of the odor similarity between one compound that contains a *cis* carbon-carbon double bond in a molecule and the other compound in which the double bond is substituted by a sulfur atom. Two feasible olfactory evaluation methods; i.e., 1) an odor similarity rating, and 2) a descriptive analysis, were employed.

If it is true that the odor-character does not significantly change in spite of such a substitution, an examination of the odorous molecules themselves is one further investigation method because the odors are based on chemical substances. The molecular features of the odorants were obtained by calculations based on quantum

chemistry.

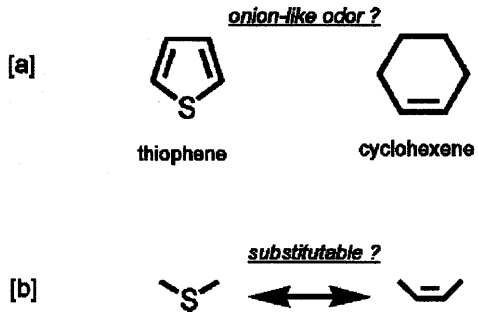


Figure 1 Molecules that contain a cis-type carbon-carbon double bond or a thioether moiety
[a] Thiophene and cyclohexene
[b] Substructures of thioether and *cis* carbon-carbon double bond

Experimental

1. Selection of odorants

Seven pairs of odorous compounds shown in Figure 2, 14 molecules in total, were selected from the literature, from our database, and by deduction from one compound that existed in the database. For every pair, one compound has a *cis* carbon-carbon double bond substructure, and the other has a thioether substructure in the molecule.

Calculation of the molecular features was performed for the seven pairs (from Pair A to Pair G). On the other hand, Pairs A, B and C, out of the seven pairs, circled in Figure 2, were further selected for olfactory evaluations. Pair A included benzaldehyde and thiophene-2-carboxaldehyde. Pair B included *cis*-3-hexen-1-ol and 2-(ethylthio)ethanol. Pair C included cyclohexene and tetrahydrothiophene. The criteria for the selection of these three pairs were toxicity to participants, material affordability, and variety of chemical structures. The three pairs are characteristic in their structures among the seven pairs; Pair A consists of aromatic ring compounds with a formyl group, Pair B consists of aliphatic compounds with a hydroxyl group, and the Pair C consists of alicyclic compounds.

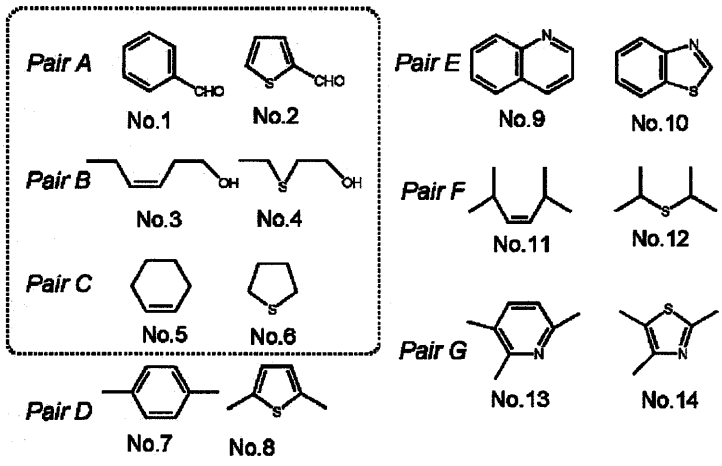


Figure 2 Selected molecules for this study

2. Selection of Participants

The participants included 19 male and 1 female university students. Their average age was 22.7 (±1.2) years old. The twenty participants were selected by a panel-screening test using the T&T olfactometer® (Daiichi Yakuhin Sangyo). The T&T olfactometer was developed and is widely used in Japan to check the human olfaction function (Takagi, 1989). Five odors such as phenylethyl alcohol ($10^{-4.0}$ w/w), 2-hydroxy-3-methyl-2-cyclopentenone ($10^{-4.5}$ w/w), isovaleric acid ($10^{-5.0}$ w/w), γ-undecalactone ($10^{-4.5}$ w/w), and 3-methyl-1H-indole (skatole, $10^{-5.0}$ w/w) were diluted by odorless liquid paraffin in the T&T. The participants were asked to select two odorous strips among 5 strips, two of which had been dipped into one of the five odorous solutions and three of which had been dipped into the odorless liquid paraffin. Each participant was requested to select two strips for a total of five times, since there were five odorous solutions. All participants in this study could correctly discriminate the two odorous strips from the three odorless strips for the 5 odors.

3. Procedure for olfactory evaluations and analysis of the evaluation data

A. Preliminary session -determination of odor intensity for evaluation and free profiling-

The odor intensity of the compounds used in the evaluation was determined according to the procedure, "intensity matching method" (Laska M, 2002). All reagent-grade chemicals were dissolved in a dilution medium, diethyl phthalate [CAS No.14189-01]. Benzaldehyde [100-52-7], thiophene-2-carboxaldehyde [98-03-3], *cis*-3-hexen-1-ol [928-96-1], 2-(ethylthio)ethanol [110-77-0], cyclohexene [110-83-8], tetrahydrothiophene [110-01-0], and 3-methylbutyl acetate [123-92-2] were purchased from Tokyo Kasei Kogyo Co., Ltd. A twenty ml aliquot of each sample was placed in a 250-ml polyethylene squeeze bottle equipped with a stopper. 3-Methylbutyl acetate (8.7g/l) was used as the reference. The odor intensities of the 6 compounds, from No.1 to No.6 in Figure 2, were adjusted to be almost equal to the intensity of the reference. The concentrations of the 6 compounds were determined as listed in Table I for the rest of the olfactory evaluations.

Nine participants among the 20 joined this session. An air-conditioned room with ventilators was used for all the olfactory evaluations in this study.

Table I Concentration of samples prepared by intensity matching method

Odorant		Conc. (g/l) in diethyl phthalate
Reference	3-methylbutyl acetate (isoamyl acetate)	8.7×10^{0}
No.1	benzaldehyde	9.6×10^{1}
No.2	thiophene-2-carboxaldehyde (stabilized with HQ)	1.9×10^{2}
No.3	cis-3-hexen-1-ol	3.2×10^{1}
No.4	2-(ethylthio)ethanol	4.8×10^{1}
No.5	cyclohexene	1.2×10^{1}
No.6	tetrahydrothiophene	9.4×10^{-2}

After determining the concentration of the chemicals, free profiling tests were performed in a different session. The participants were asked to describe the odor qualities of the six compounds and a reference using their own words. "Seaweed, laver", "pickled Japanese radish, salted pickled vegetables", "adhesive (quick-drying glue), paint, marker", and "rubber" were selected as the new groups of descriptive terms. Harper's 44 descriptors

(Harper, 1968) and the four additional descriptors, 48 descriptors in total (Table II), were used for the odor quality profiling.

Table II Forty-four Descriptors (adopted from Harper, 1968) and 4 additional descriptors used for profiling odor quality

No	Odor Descriptor	No	Odor Descriptor
1	aromatic	25	almond-like
2	meaty (cooked)	26	burnt, smoky
3	sickly	27	herbal, green, cut grass, etc.
4	musty, earthy, moldy	28	etherish, anaesthetic
5	sharp, pungent, acid	29	sour, acid, vinegar, etc.
6	camphor-like	30	like blood, raw meat
7	light	31	dry, powdery
8	heavy	32	like ammonia
9	cool, cooling	33	disinfectant, carbolic
10	warm	34	oily, fatty
11	metallic	35	like mothballs
12	fruity (citrus)	36	like petrol, solvent
13	fruity (other)	37	cooked vegetables
14	putrid, foul, decayed	38	sweet
15	woody, resinous	39	fishy
16	musk-like	40	spicy
17	soapy	41	plant-like
18	garlic, onion	42	rancid
19	animal	43	minty, peppermint
20	vanilla-like	44	sulfurous
21	fecal (dung-like)	45	seaweed, laver
22	floral	46	pickled Japanese radish, salted pickled vegetables
23	fragrant	47	adhesive (quick-drying glue), paint, marker
24	sweaty	48	rubber

B. Direct ratings of odor similarity

The similarity in the odor qualities was directly evaluated by a pair-wise comparison without employing any verbal expression. A pair of odors was presented, and participants freely smelled the two samples. The similarity in a pair of odors perceived by a participant was marked on the 10 cm arrow without graduations; the length of 0 cm from the left-end means that the pair of odors was perceived to be completely different, while the length of 10 cm from the left-end means the pair of odors was perceived to be exactly the same. The average length marked by 20 participants was calculated for each pair, and defined as the Odor Similarity Score (OSS) for a pair of compounds. The 10 cm corresponds to an OSS of 100%, whereas 0 cm corresponds to an OSS of 0%. The time-interval from the end of the former judgment of one pair (ex. No.1 and No. 2) to the next presentation of another pair (ex. No.3 and No.4) was about 90 seconds.

In the same session, the participants were also asked to select the perceived strength of the odors from 5 different rankings (not detectable, weak, medium strength or easily recognizable, rather strong, very strong) in order to check whether the participants could easily recognize the odors.

C. Odor quality profiling using descriptive terms

The 48 descriptors (Table II) were presented in the Japanese language. The intensity of each odor descriptor was rated using a 6-point scale (0:not at all - 5:extremely).

The ratings of each descriptor by each participant were then summed. Pearson's correlation coefficient (r) between the sums for each descriptor in each pair was calculated. The similarity of the profiling data of each pair was judged by the coefficient r. The descriptors were analyzed by a component analysis. SPSS software (SPSS Inc.) was used for the calculations.

4. Calculation and analysis of molecular features

The molecular structures of 14 compounds in Figure 2 were constructed using CS ChemDraw Ultra (ver. 5.0, CambridgeSoft Corporation, USA) and CS Chem3D Pro (ver. 5.0, CambridgeSoft Corporation, USA). Conformations of the chain-type molecules (Pair B) were analyzed using Conflex (ver. 4.02, rev. I, Conflex Corp. and GOTOH, Japan) and Barista (ver. 1.0.0.3, Conflex Corp. and GOTOH, Japan). The three-dimensional structures were optimized by the MP2/6-31G(d, p) method using Gaussian 98 (Revision A.7, Gaussian, Inc., USA) (Frish et al., 1998). Superimpositions of the optimized molecular structures of each pair were performed by the Root Mean Square (RMS) fit in Quantum CAChe (ver. 3.2, Oxford Molecular, Ltd., U.K.). The carbon and oxygen atoms that are common in the two molecules in each pair were superimposed. No atoms in the *cis* double bond or the sulfur atom were used for the superimposition.

The dipole moments and partial charges (Mulliken, ChelpGreneman) were calculated by MP2/6-31G(d,p) as electronic features of the molecules. The electrostatic potentials were analyzed using MolStudio (R3.1, NEC Corporation, Japan).

Results

1. Odor similarity of the three pairs

From the direct rating of the odor similarities, the Odor Similarity Scores (OSS) for the three pairs with the standard error (±S. E.) are shown in Figure 3. The OSS of the identical compounds, which is 3-methylbutyl acetate, was 90%. The average OSS between the benzaldehyde and thiophene-2-carboxaldehyde of Pair A was 61%, whereas the OSS between the *cis*-3-hexen-1-ol and 2-(ethylthio)ethanol of Pair B was 11%. In the case of Pair B, the participants noticed a very significant difference between the two odors.

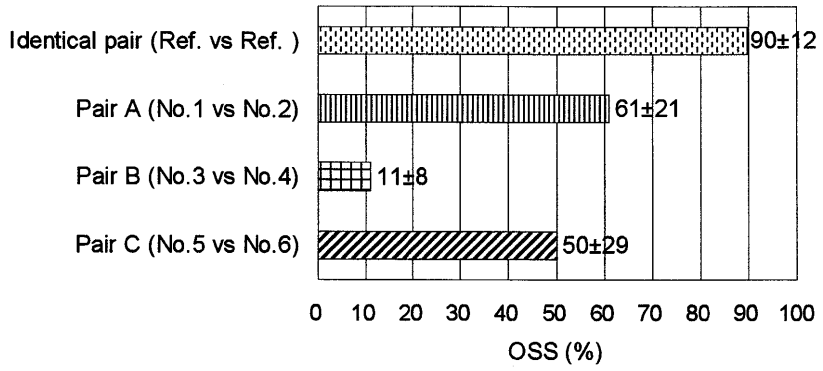


Figure 3 Averaged Odor Similarity Score (OSS) of Pairs A, B, and C ±S. E.

As a result of the component analysis, 74% of the descriptors were explained by the two components. One could be called the pleasant & unpleasant axis, and the other could be called the natural & artificial axis. Based on the profiling data, the 6 odors were expressed in the two dimensional plane (Figure 4). The compounds containing sulfur atom in each pair are always less pleasant than the non-sulfur compounds. The existence of a sulfur atom in the molecules adds an unpleasant nuance to the odor qualities in the three cases. The patterns obtained by profiling, based on the sum of the ratings, are shown in Figure 5. The correlation coefficients (r) of the bar graphs for each pair of odors are also indicated in Figure 5. Regarding the similarity of the odors, the OSSs (Figure3) coincide with the correlation coefficients (r), which were calculated from the profiling patterns (Figure 5). The distances between the odors in each pair (Figure 4) also agree with the OSS (Figure 3) and the profiling patterns (Figure 5). Therefore, we judged that the odors from pair A are the most similar and that those of Pair B are the least similar among the three pairs. It was concluded that not in all the cases, but in some cases, that the substitution of the *cis* -C=C- moiety for the sulfur atom in a molecule does not produce a big change in the odor quality.

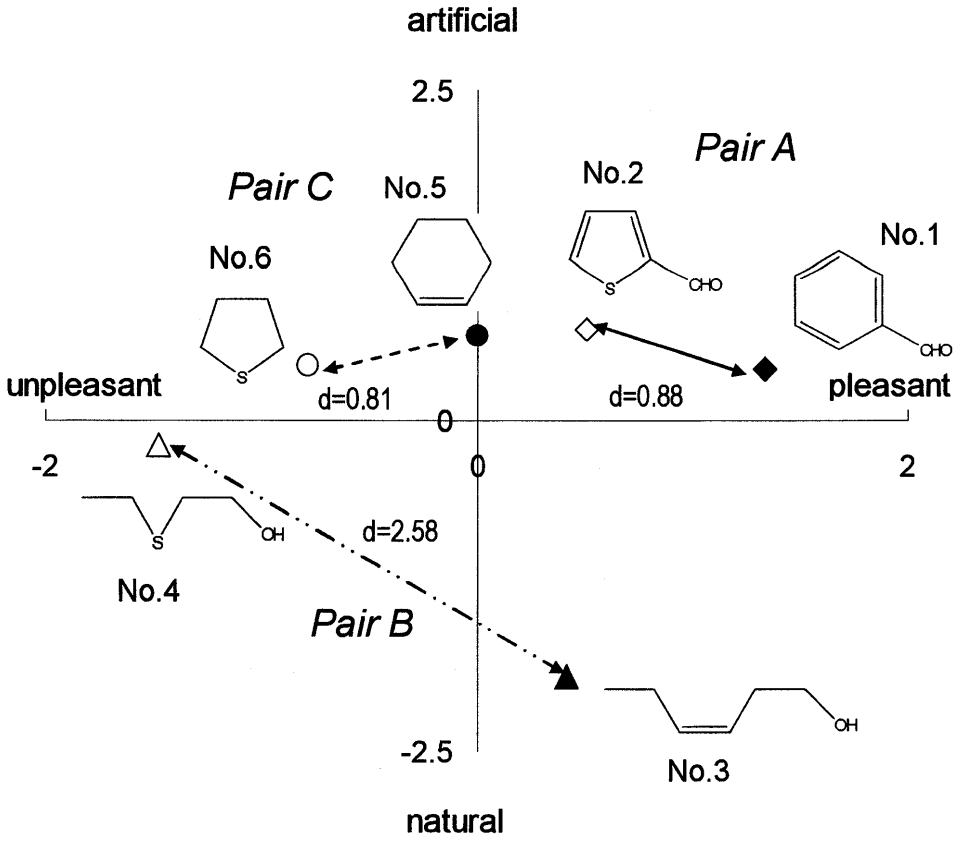


Figure 4 Distances for the two compounds in Pairs A, B, and C based on the component analysis of the profiling data

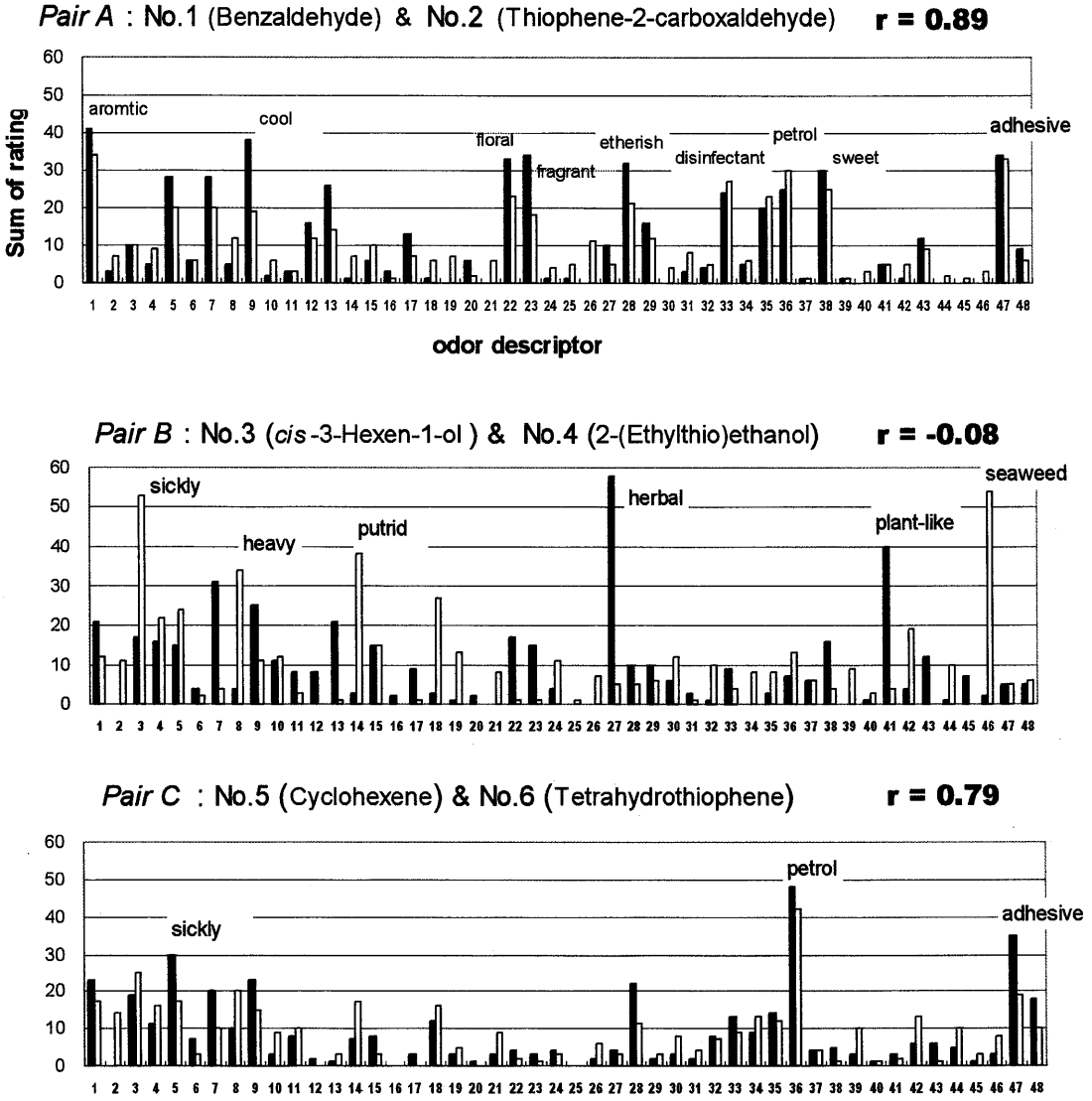


Figure 5 Profiling patterns of 6 odors and Pearson's correlation coefficient (r) for each pair
■ for cis C=C
□ for -S-

2. Comparison of calculated molecular features

The results from the olfactory evaluations and molecular orbital calculations are summarized in Table III.

Table III Odor similarity and the difference in the calculated molecular features
(The smallest value in each row is underlined, and the largest value is written in italics)

Odor	Pair		Difference of molecular features RMS	Dipole moment	Mulliken	CHELPG	ESP(max)*	ESP(min)**
similar	A	*No.1* vs. *No.2*	**0.045**	**0.07**	*0.31*	**0.02**	44	**0.0017**
↕	C	*No.5* vs. *No.6*	0.065	*2.10*	**0.12**	0.08	**6**	*0.0090*
different	B	*No.3* vs. *No.4*	*0.170*	0.91	0.22	*0.13*	*73*	0.0073

* ESP(max) : the highest value of the electrostatic potential
** ESP(min) : the lowest value of the electrostatic potential

Which molecular features contribute to the odor similarity? It is considered that the similarity in the odor qualities (judged from olfactory evaluation) is related to the RMS values and the difference in the ChelpGreneman (CHELPG) (Breneman and Wiberg, 1990) charges between the pairs. The difference in the RMS values and the difference in the CHELPG charges of the three pairs are shown by the bar graph in Figure 6.

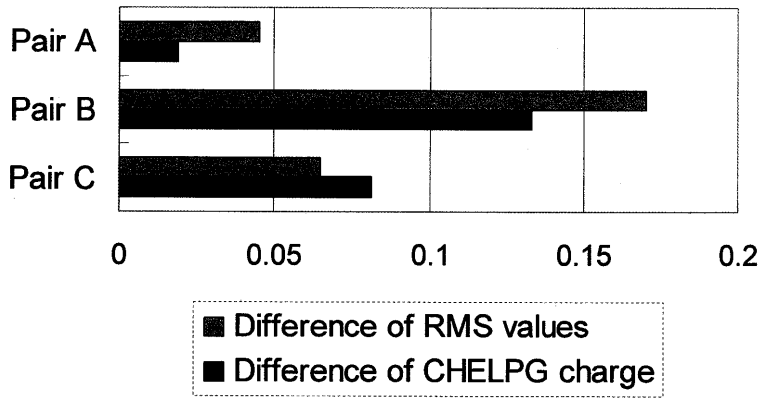


Figure 6 Difference in RMS values and CHELPG charges of the three pairs

A small value RMS denotes a similarity in the molecular structures. The CHELPG charge is a type of charge, which reflects the electrostatic potential. Superimposed images of the three pairs are shown in Figure 7. The 3D structures of the compounds in Pair A, and those in Pair C are very similar. The CHELPG charges of the carbon atoms and attached hydrogen atoms in the *cis* -C=C-, and of the sulfur atom in the thioether moiety are shown in Figure 8. Images of the electrostatic potentials expressed by MolStudio are shown in Figure 9.

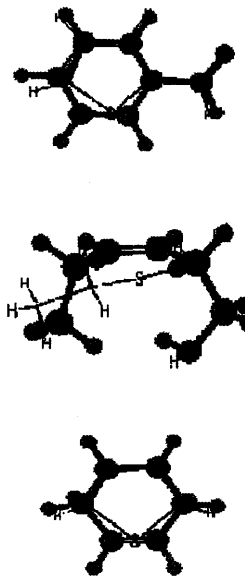


Figure 7 Superimposed structures of the three pairs (Pairs A, B, and C from the top)
(The carbon and oxygen atoms that are common in the two molecules in each pair were superimposed.)

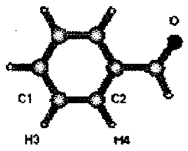
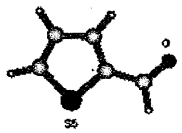
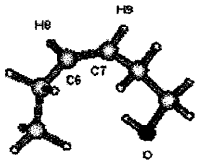
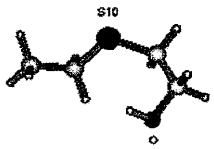
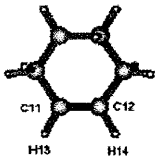
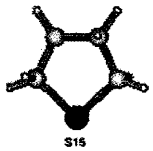
							S	Δ
No. 1	No. 2		No. 1		No. 2			
			atom C1	-0.01	atom S5	0.00		
			C2	-0.20				
			H3	0.08				
			H4	0.11				
			Σ	-0.02	Σ	0.00		0.02
No. 3	No. 4		No. 3		No. 4			
			atom C6	-0.28	atom S10	-0.35		
			C7	-0.14				
			H8	0.10				
			H9	0.09				
			Σ	-0.22	Σ	-0.35		0.13
No. 5	No. 6		No. 5		No. 6			
			atom C11	-0.21	atom S15	-0.30		
			C12	-0.21				
			H13	0.10				
			H14	0.09				
			Σ	-0.22	Σ	-0.30		0.08

Figure 8 CHELPG charges of the atoms in the cis -C=C- double bond and of a sulfur atom in the thioether moiety (The sum (∑) of the charges and their differences (Δ) in the three pairs. The sulfur atom is indicated in black, and the oxygen atom is indicated as the letter "O" in the figure.)

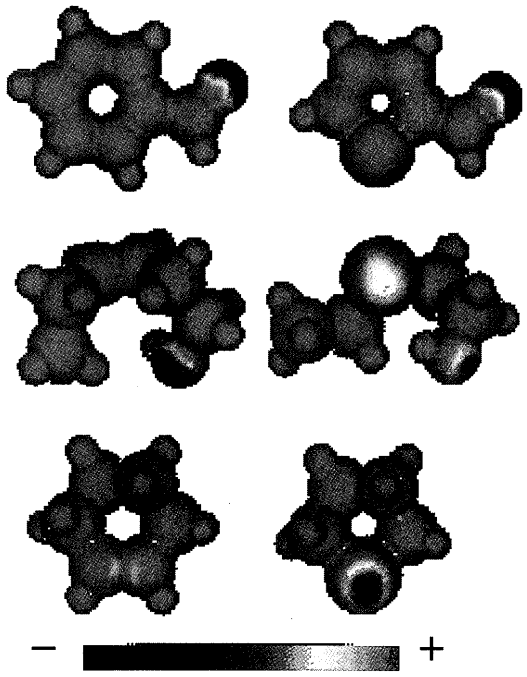


Figure 9 Electrostatic potential images of the six compounds (Pairs A, B, and C from the top)

It could be concluded that the odor qualities are similar when the entire molecular structures and electrostatic features of the substituted parts (-C=C-, -S-) are similar. In other words, instead of constituent atoms in a pair of odorous molecules, the similarity of the molecular structures (shapes) and electrostatic potentials determine the similarity of the odor qualities of the pair.

The RMS values and difference in the CHELPG of the 8 compounds for the remaining pairs (Pair D to Pair G), not used for the olfactory evaluations, are shown in Table IV.

Table IV Expected of odor similarity of the other calculated pairs

		Difference of molecular features		Expectation of Odor Similarity
Pair		RMS	CHelpG	
D	*No.7* vs. *No.8*	0.082	0.07	
E	*No.9* vs. *No.10*	**0.065**	**0.00**	← most similar of these 4 pairs
F	*No.11* vs. *No.12*	*0.38*	*0.11*	
G	*No.13* vs. *No.14*	0.086	0.03	

The odors in Pair E (No.9 and No.10) are deduced to be the most similar of the four pairs based on the results in Table III. No.10, benzothiazole, is described as "quinoline-like" in the literature (Indo, 1996), whereas No.9 is quinoline itself. This study is not a quantitative one, but would help to predict odor similarities between one odorant and another odorant with a small substitution in their structures.

Discussion

1. Importance of the odor similarity (and odor quality) measurements

There is no objective, simple, and general method available for the quantification of odor quality (for review, see Wise et al., 2000). Verbal odor descriptors were excluded in the direct ratings of the similarity by a pair-wise comparison, as the first evaluation method in this study. Limited numbers of verbal descriptors were used in profiling, as in the second method. These two methods were applied as a feasible approach. We considered it possible to judge the tendency of the odor similarity for a pair of odors from the agreements between the results obtained by the two methods. Fortunately, the results from the two types of evaluations were not contradictory.

A combination of these methods is considered to be effective for obtaining more reliable data than the mere odor quality descriptions in the literature, though the methods are still subjective.

The relation between the odorants and odor qualities are still not entirely understood. One of the reasons that prevents the progress in the quantitative or qualitative structure-odor relationship studies is that reliable odor evaluation data are quite limited. It is indispensable to measure the similarity between the odor qualities. More emphasis should be put on the actual measurement of odors, even though a perfect method does not exist.

2. Importance of electronic features in odorant molecules

Today, it is considered that complementarity between olfactory specific proteins and odorant molecules is required to trigger a further transduction in the olfactory system. Molecules must well fit into proteins. However, the detailed primary odor reception mechanism still remains one of the unresolved areas in olfaction.

Through the research studies of the Structure-Odor Relations (SOR) or Quantitative Structure-Activity Relationships (QSAR) of odor, the molecular properties strongly related to odor sensation have been explored. In Comparative Molecular Field Analysis: CoMFA) (Cramer, 1988), structural as well as electrostatic features were regarded as important factors. CoMFA was applied to many studies of odoriferous compounds (Yoshii and Hirono, 1996; Rossiter, 1996; Buchbauer et al., 2000). Gorbachov et al, who noticed the importance of the electronic features and spatial position of atoms, introduced the electronic-topological method. This method continues to be applied for their analyses (Gorbachov and Rossiter, 1999). Rognan and Chastrette (1994) noticed hydrogen bonding and dispersion forces between odorous molecule and receptors.

In this study, similarities in the odor qualities are mainly explained by the similarities in both the structural and electrostatic features of the compounds. This result affirmed the CoMFA and Gorbachov's approaches.

On the other hand, Turin assumed that receptor proteins detect the vibration of odorous molecules through a plausible mechanism, i.e., biological inelastic tunneling (IETS) (Turin, 1996). His equation was comprised of squares of point charges, though they are not the electrostatic ones. The charges or electrons would play an important role in odor reception. Accordingly, the study not relying on atom types, but placing more emphasis on the electrons in odorous molecules, will promote not only the SOR and QSAR studies, but also an elucidation of the primary odor reception mechanism.

Acknowledgements

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