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Construction of a Quantitative Three-dimensional Model for Odor Quality using Comparative Molecular Field Analysis (CoMFA)

Fumiko Yoshii and Shuichi Hirono

School of Pharmaceutical Sciences, Kitasato University, 5–9–1 Shirokane, Minato-ku, Tokyo 108, Japan

Correspondence to be sent to: F. Yoshii, School of Pharmaceutical Sciences, Kitasato University, 5–9-1 Shirokane, Minato-ku, Tokyo 108, Japan

Abstract

A quantitative structure-activity relationship (QSAR) study of odorants was performed taking an odor as an activity. As an example, we took the 'green odor of pyrazine derivatives' as an activity. Conformational analysis of the pyrazine derivatives was performed, and conformers were selected using the longest side-length of a circumscribed box (LLCB) as a criterion. Comparative molecular field analysis (CoMFA) was used to elucidate the three-dimensional (3D) structural features of the derivatives. As a result, it was found that the steric and electrostatic features of the derivatives were correlated with human olfactory detection threshold values. We constructed a quantitative 3D model using the graphic views of CoMFA and partial structures of the derivatives. The prediction of human olfactory detection threshold values of other pyrazine derivatives with green odor was possible by using the 3D model. As another example, we took the 'sweet odor of compounds with various structures' as an activity. A quantitative 3D model for sweet odor was constructed in the same manner. Analysing the structural features of odorants by CoMFA and constructing 3D models for several important odor qualities would help to (i) explain or predict human olfactory detection threshold values of interesting odorants, (ii) design new odorants by suggesting the steric and electrostatic requirements, and (iii) elucidate the mechanism of odorant-receptor interaction.
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Introduction

A quantitative structure-activity relationship (QSAR) study aims to correlate 'molecular features including structures' with 'activity'. The idea of the QSAR study is that molecules provide information necessary for understanding biological activities. The advantage of this idea is that we can explain activities by molecular features, even though information about the receptor is quite limited. We focused on odorants in this research. As for odor, there are many kind of activities, because there are multiple odor qualities.

The QSAR studies of musk odor have been widely performed and various models have been proposed (Yoshii *et al.*, 1992; Pelzer *et al.*, 1993). For other odor qualities, the study of sandalwood odor by Buchbauer *et al.* (1994) and of bell-pepper note by Rognon and Chasterette (1994) were recently performed. When a good correlation between the three-dimensional (3D) structural features of odorants and odor strength of an odor quality is found, one is able to propose a 3D model for the odor quality. The model is a criterion or a standard expressing molecular features for odorants with a certain odor quality. Most of the models for

odor qualities, so far, can judge whether an odorant has a specific odor quality and whether the specific odor is strong, but these can not estimate actual human olfactory threshold values of odorants for the specific odor.

The aim of this research is to elucidate 3D structural features of odorants and to construct a quantitative 3D model for a certain odor quality. We took two odor qualities as examples. One quality was the 'green odor of pyrazine derivatives'. The other quality was the 'sweet odor of compounds with various structures'.

The method to construct 3D models should be an easy and applicable one for a wide range of odorants. Comparative Molecular Field Analysis (CoMFA; Cramer *et al.*, 1988) has been used for the 3D QSAR study, and successfully applied to many pesticides (Calder *et al.*, 1993; Akamatsu *et al.*, 1994) and drugs (DePriest *et al.*, 1993; Horowitz *et al.*, 1993; Krystek *et al.*, 1994). CoMFA correlates the difference in compound activity to the difference in the steric and electrostatic features of compounds by calculating interaction energies between atoms in compounds and 'probe atoms' placed at the 3D lattice that surrounds the compounds. We used the result of CoMFA, which is viewed by graphical output, to construct a quantitative 3D model. The 3D model is expected to reflect the steric and electrostatic features of odorants with a specific odor quality.

Materials and methods

The procedure for this work is shown in Figure 1. All the calculations except the longest side-length of circumscribed box (LLCB) and 1-octanol/water partition coefficient (log P) were performed on a SiliconGraphics IRIS 4D/420GTX using SYBYL (Ver. 6.0a). The LLCB was calculated by our self-written program on the same workstation. The LLCB was first introduced as 'the longest side-length of a hexahedron that circumscribed the van der Waals surface of a molecule' in our previous work (Yoshii *et al.*, 1991). Log P was calculated by MlogP (Moriguchi *et al.*, 1994) on an Apple Macintosh Quadra 700.

Example 1. Green odor of pyrazine derivatives

Selection of odorants and of threshold values

We selected pyrazine derivatives having a green odor based on Shibamoto's report (1986). We also used the human olfactory detection threshold values in water from his report.

Construction of structures, conformational analysis and selection of conformers

Structures of odorants were constructed and minimized by molecular mechanics calculations using Tripos force field parameters in the SYBYL QSAR module.

Conformational analyses were performed using Random Search (Saunders, 1987). Standard criterion for the search is: maximum cycle is 3000 times; root mean square deviation (RMS) threshold is 0.5 Å; energy cut-off is the energy of the first minimized conformer of each compound plus 5 kcal/mol; energy convergence is 0.05 kcal/mol. The maximum cycle was increased to 10 000 times by checking the number of single-hit conformers through the whole search. The RMS threshold of 0.3 Å was also used in the case of compounds with a small flexibility and the result was taken into consideration.

It is very important to select an active conformer from the energy-stable conformers of a compound. A stable and compact conformer was considered to be similar to the olfactory active conformer in our previous works Yoshii *et al.*, 1993, 1994). LLCB is a good parameter to characterize the compactness of a molecule. The LLCB of each conformer was calculated and conformers having the LLCB within the shortest LLCB plus 1 Å were selected when there were more than 10 conformers that were searched using conformational analysis. The selected conformers were used for further analysis.

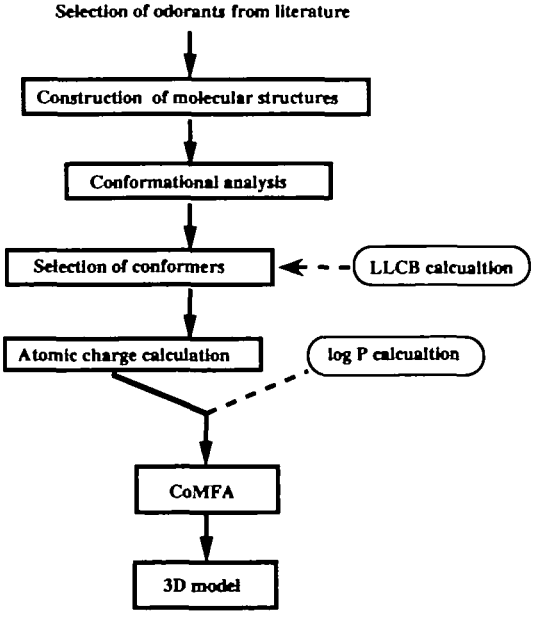

Figure 1 Procedure to obtain a 3D model using CoMFA.

Analysis of odorants using CoMFA

The idea of CoMFA is that the difference in the activity of compounds relates to the difference in the steric and electrostatic features of the compounds, as mentioned in the Introduction. 'Probe atoms' are placed at the 3D lattice points which surround the compounds. The steric (Lennard–Jones) and electrostatic (coulombic) interaction energies between atoms in the compounds and 'probe atoms' are calculated. Atomic charges of selected conformers were calculated using the PM3 method (Stewart, 1992). The used 'probe atom' had van der Waals properties of an sp3 carbon atom and its charge was +1.0. The lattice points were separated by 2 Å and the number of lattice points varied according to the size of the largest compound in a data set. The conformers were aligned by least-squares fitting focusing on the substructure of the compounds. Position and orientation of the conformers are important, since 'probe atoms' are set at the fixed lattice points and the interaction energies at the lattice points are calculated. The cut-off value for steric interaction was 30.0 kcal/mol and for electrostatic interaction was 30.0 kcal/mol as an absolute value. Any value that exceeded cut-off values were replaced by the cut-off values.

The interaction energies at the lattice points and calculated log P values were used as parameters. The partial least-squares (PLS) method (Cramer *et al.*, 1988) was used for statistical analysis. PLS is a new regression technique, which is likened to principal components analysis. The optimum number of components was determined to be that which yielded the lowest standard error of predictions and the high leave-one-out r^2. Leave-one-out evaluates the predictive ability of a model; the analysis with excluding one compound from a data set is repeated till every compound is excluded one time; human olfactory detection threshold values of every excluded compound is predicted by the resulting model of the subset of the compounds. Selection of the final conformers was done by focusing on their 3D structures and on the residual values between the actual and predicted values by PLS analysis.

Construction of 3D model using the result of CoMFA

The steric and electrostatic coefficients for each probe atom were calculated, and components that contributed to activity were extracted by CoMFA-PLS. The result was viewed using a contour map of 'standard deviation×coefficient'. Eighty percentiles and twenty percentiles for both the steric and electrostatic contribution were used to draw the contours. The contour maps and partial structure of odorants in the analysis were used to construct the 3D model. The orientation of the partial structure was made to match the alignment of the odorants for analysis by CoMFA.

Example 2. Sweet odor

Compounds with a sweet odor and their human olfactory detection threshold values in water were selected from several different studies, not from a single one. The odorants in Example 2 did not have a common ring structure as did the pyrazine derivatives in Example 1. Non-active compounds (compounds without a sweet odor) were included into this analysis. The other procedures were the same as above.

Results

Example 1. Green odor of pyrazine derivatives

Analysis of green odor of pyrazine derivatives by CoMFA

Nine pyrazines (Figure 2, Table 1) were used for the analysis. After conformational analysis, 54 conformers of nine pyrazine derivatives were selected using LLCB as a criterion. The conformers were aligned by least-squares fitting of a pyrazine ring by putting one common methyl group in the same direction. The number of automatically generated probe atoms was 810. Therefore, 1620 data for both the steric and electrostatic interaction energies were calculated, and were analyzed by PLS with the calculated log P.

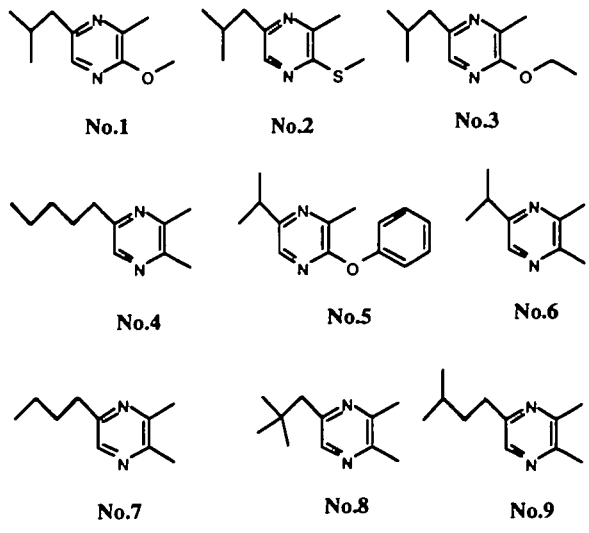

Figure 2 Structures of selected pyrazine derivatives with green odor.

Table 1 Selected pyrazine derivatives, their odor description and human olfactory detection threshold values

No.	Pyrazine	Odor description	Threshold value in water (p.p.m.)
1	5-isobutyl-2-methoxy-3-methyl-	Green	0.00018
2	5-isobutyl-3-methyl-2-methylthio-	Muddy green	0.015
3	2-ethoxy-5-isobuthyl-3-methyl-	Green fruity	0.016
4	5-pentyl-2,3-dimethyl-	Cocoa green	0.09
5	5-isopropyl-3-methyl-2-phenoxy-	Woody, green	0 37
6	5-isopropyl-2,3-dimethyl-	Herbal green	0.53
7	5-butyl-2,3-dimethyl-	Sweet, green	0.77
8	5-neopentyl-2,3-dimethyl-	Green	3.00
9	5-isopentyl-2,3-dimethyl-	Green	6.00

A good CoMFA-PLS result was obtained, when nine conformers out of 54 conformers were selected by focusing on their 3D structures and on the residual values between the actual and predicted values using PLS analysis. The result is shown in Table 2. The r^2 with the leave-one-out validation is 0.759, and the r with the leave-one-out validation is 0.871. The model is predictive and robust, since the probability of a chance correlation is found to be 5% or less for a validated r^2 of 0.3 or greater (Clark *et al.*, 1990). The calculated log P values were not effective parameters. Therefore, the human olfactory detection threshold value of the green odor is explainable based on the steric and electrostatic features of the odorants.

Table 2 CoMFA-PLS result of pyrazine derivatives with green odor

Number of compound	9
Number of component	2
r^2 (leave-one-out)	0.759
r (leave-one-out)	0.871
r^2 (no validation)	0.968
r (no validation)	0.984
F values (n_1 = 2, n_2 = 6)	91.423
Standard error of estimate	0.288
Probability of r^2=0	0.000
Steric/electrostatic contribution	0.759/0.241

3D model for the green odor of pyrazine derivatives

The 3D model for the green odor of the pyrazine derivatives is proposed in Figure 3. The model consists of (i) steric and electrostatic contour maps by the CoMFA, and (ii) a pyrazine ring and one carbon atom in the methyl group that are common in the pyrazine derivatives. To make it easy to see, the model is divided into a steric part (3-S) and an electrostatic part (3-E) in Figure 3. Figure 3-S indicates that introduction of bulky substructures or groups near the black contour regions would increase the odor strength (lower human olfactory detection threshold value). On the contrary, bulkiness is unfavored near the gray contour region to increase the odor strength. Figure 3-E indicates that introduction of a substructure or a group with a negative charge, like a functional group contains an oxygen atom, in the direction of the black contour region is favored to increase the odor strength. The steric and electrostatic features of the strongest odorant in the data set, 5-isobutyl-2-methoxy-3-methyl pyrazine (No. 1), matches the 3D model as seen in Figure 4.

Five pyrazine derivatives of racemic mixtures were selected from the same report (Shibamoto, 1986) and used to check the prediction ability of the model. Conformers of both R and S configurations of the five were constructed and superimposed on the partial ring structure in the 3D model. Prediction of the activity can be performed promptly in the SYBYL QSAR module. The human olfactory detection threshold values of the five were predicted as listed in Table 3. The lowest predicted threshold values are shown in the table, because an active conformer is considered to give the lowest threshold value. Three pyrazine derivatives out of five were successfully predicted by the 3D model.

Example 2. Sweet odor

Analysis of compounds with a sweet odor by CoMFA

We selected 10 compounds with a sweet odor and two structurally similar ones without a sweet odor (Figure

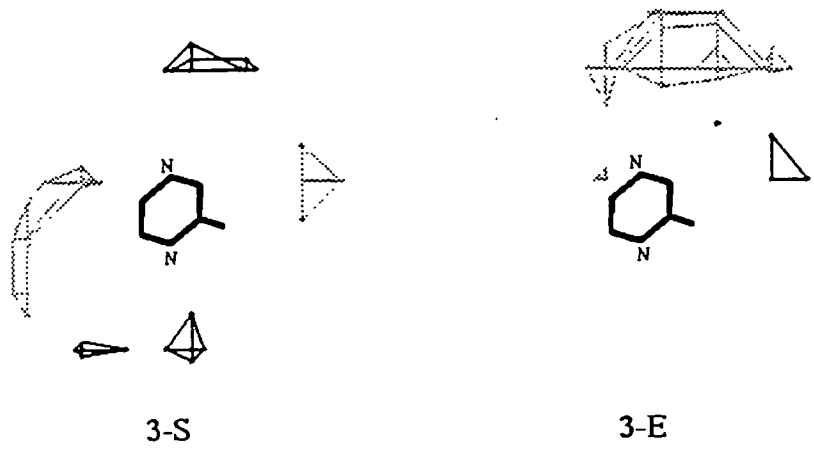

Figure 3 3D model for the green odor of pyrazine derivatives (3-S) Steric information—black contour: steric favored; gray contour: steric unfavored. (3-E) Electrostatic information—black contour. negative charge favored, gray contour negative charge unfavored

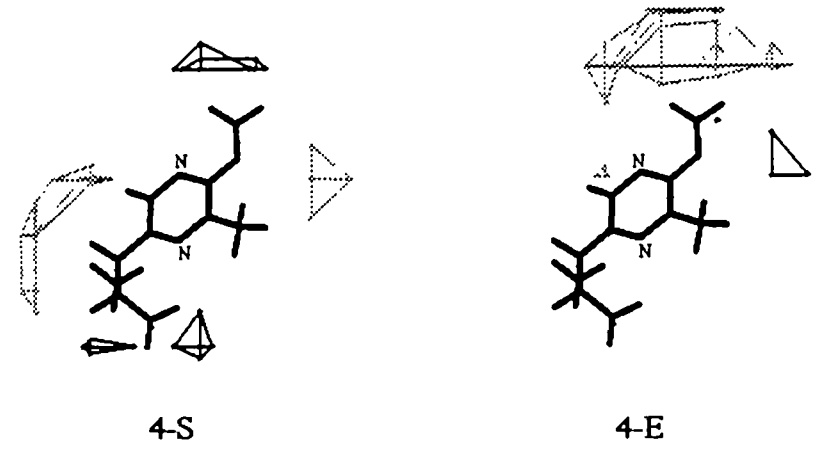

Figure 4 5-isobutyl-2-methoxy-3-methyl pyrazine (No 1) with the 3D model for green odor (4-S) Steric information—black contour: steric favored, gray contour: steric unfavored. (4-E) Electrostatic information—black contour negative charge favored, gray contour: negative charge unfavored

Table 3 Prediction of human olfactory detection threshold values of other pyrazine derivatives with green odor by 3D model

Pyrazine	Odor description in literature	Actual threshold values: log (1/threshold value)	Calculated threshold values: log (1/threshold value)	
			R configuration	S configuration
2-methoxy-3-methyl-5-(2-methylbutyl)-	Green, leather	11	9.1	9.0
2-ethylthio-3-methyl-5-(2-methylbutyl)-	Green, roast	8.6	8.5	7.6
2-ethoxy-3-methyl-5-sec-butyl-	Fruity green	7.9	9.7	9.1
3-methyl-5-(2-methylpentyl)-2-methylthio-	Fatty green	7.9	7.5	8.0
5-(1-methylbutyl)-2,3-dimethyl-	Woody, green	6.1	6.7	6.7

5) from different studies (Hodge, 1967; Arctander, 1969; Kobayashi, 1989). Their human olfactory detection threshold values in water from different sources (Helbig, 1939; Cartwright and Kelley, 1952; Pyysalo *et al.*, 1977; Engel *et al.*, 1988; Kobayashi, 1989; Bingham *et al.*, 1990; Nishimura and Mihara, 1990) were rounded off to one

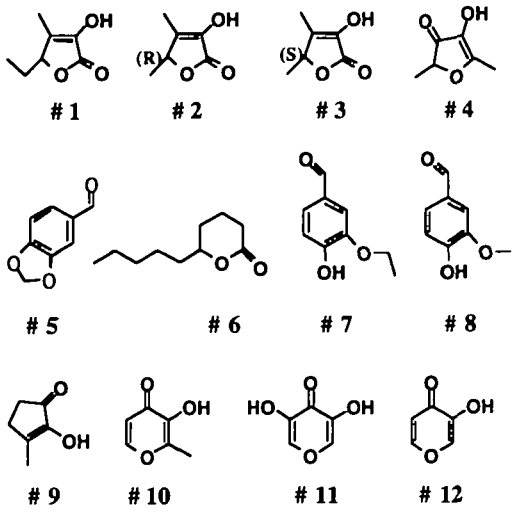

Figure 5 Structures of selected compounds with sweet odor (Nos 1–10) and without sweet odor (Nos 11 and 12).

significant figures and are shown in Table 4. The high threshold value, 100, was used for convenience for the two compounds without a sweet odor.

Seventy-one conformers of 12 compounds were selected using LLCB as a criterion. The conformers were aligned using 3-hydroxy-2-methyl-4-pyrone (No. 10) as a reference by least-squares fitting focusing on two neighboring oxygen atoms and the carbon atoms connecting them. We focused on the two neighboring oxygen atoms, though the requirement of functional groups for sweet odor compounds is not clearly understood. The number of probe atoms automatically generated were 512 in this case. A good CoMFA-PLS result was obtained using 13 conformers of 12 compounds. Thirteen conformers were selected, because the two conformers of 3,5-dihydroxy-4-pyrone (No. 11) must have high threshold values. The human olfactory detection threshold value of

Table 4 Selected compounds, their odor description, human olfactory detection threshold values and references

No.	Name of compounds	Odor description	Ref.	Threshold values in water (p.p.m)	Ref.
1	5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone	A burnt sugary aroma	Kobayashi (1989)	0.00000001	Kobayashi (1989)
2	(R)-3-hydroxy-4,5-dimethyl-2(5H)-furanone	A burnt sugary aroma	Kobayashi (1989)	0.000001	Kobayashi (1989)
3	(S)-3-hydroxy-4,5-dimethyl-2(5H)-furanone	A burnt sugary aroma	Kobayashi (1989)	0.000001	Kobayashi (1989)
4	4-hydroxy-2,5-dimethyl-3(2H)-furanone	Caramel, sweet, fruity	Arctander (1969)	0.00004	Pyysalo *et al.* (1977)
5	3,4-methylenedioxybenzaldehyde	Very sweet floral, warm slightly spicy and tenacious odor	Arctander (1969)	0.06	Helbig (1939)
6	δ-decalactone	Very powerful and very tenacious, sweet creamy, nut-like odor with a heavy fruity undertone	Arctander (1969)	0.1	Engel *et al.*(1988)
7	3-ethoxy-4-hydroxybenzaldehyde	Intensely sweet odor, warm, slightly floral and with some resemblance to vanilla in its creamy sweetness	Arctander (1969)	0.1	Cartwright and Kelly (1952)
8	4-hydroxy-3-methoxybenzaldehyde	Intensely sweet and very tenacious creamy-vanilla-like odor	Arctander (1969)	0.2	Cartwright and Kelly (1952)
9	2-hydroxy-3-methyl-2-cyclopenten-1-one	Sweet and very powerful, caramellic-spicy odor	Arctander (1969)	0.3	Nishimura and Mihara (1990)
10	3-hydroxy-2-methyl-4-pyrone	Warm-fruity, caramellic-sweet odor	Arctander (1969)	30	Bingham *et al.* (1990)
11	3,5-dihydroxy-4-pyrone	Not sweet	Hodge (1967)	100	—
12	3-hydroxy-4-pyrone	Not sweet	Hodge (1967)	100	—

the sweet odor is correlated with the steric and electrostatic features of the odorants, as seen in Table 5. Calculated log P values were again not an effective parameter.

3D model for sweet odor

The 3D model for sweet odor (Figure 6) is proposed in the same manner as Example 1. The model consists of (i) steric and electrostatic contour maps by the CoMFA and (ii) a planar six-membered ring of carbon atoms with two oxygen atoms. The planar six-membered ring with oxygen atoms is an imaginary structure and used for the model, since the other ring structures of Figure 5 were considered and 3-hydroxy-2-methyl-4-pyrone (No. 10) was most convenient for superimposition of the other compounds. A hydrogen atom in the model is shown in parenthesis, because the atom is not always necessary. The compound of the strongest odor, 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone (No. 1), is not contradictory to this 3D model as seen in Figure 7-S, but does not seem to fit Figure 7-E. This does not mean that the model obtained here is not reliable, because the contours reflect the result of the whole data set and give indication to increase the activity by the steric and electrostatic features of the molecules.

Human olfactory detection threshold values of 2-ethyl-3-hydroxy-4-pyrone and 5-propenyl-2-ethoxyphenol were predicted using the 3D model. Two neighboring oxygen atoms in the hydroxy group and methoxy or ethoxy group, and two carbon atoms connecting the oxygen atoms were used for superimposition on the partial structure in the 3D model. Predicted human olfactory detection threshold values and actual threshold values of odorants for comparison are shown in Table 6. The data concerning strength of the odor, cited from Arctander's literature (1969) are shown in the table, since reliable human olfactory detection threshold values of the two odorants are not currently available. The ranking of odor strength of the two odorants was correctly predicted.

Table 5 CoMFA-PLS result of compounds with sweet odor

Number of compound	12
Number of component	3
r^2 (leave-one-out)	0.771
r (leave-one-out)	0.878
r^2 (no validation)	0.981
r (no validation)	0.990
F values (n_1 = 3, n_2 = 9)	154.414
Standard error of estimate	0.864
Probability of r^2 = 0	0.000
Steric/electrostatic contribution	0.679/0.321

Discussion

Selection of conformers of odorants

We could construct 3D models using some of the stable and compact conformers. Therefore, simple selection of conformers focused on LLCB is effective, though we should reconsider the criterion, the shortest LLCB plus 1Å.

For selection of the final conformer set for the model, we tried various conformer sets based on 3D structures and the residual values between the actual and predicted values by PLS. The more simple method to select the final conformer set is desirable.

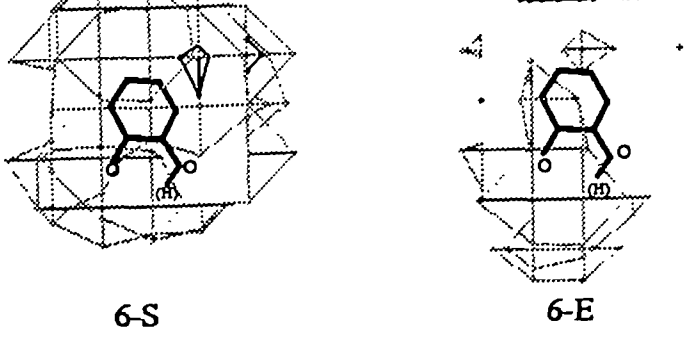

Figure 6 3D model for sweet odor (6-S) Steric information—black contour: steric favored; gray contour: steric unfavored. (6-E) Electrostatic information—black contour: negative charge favored; gray contour: negative charge unfavored.

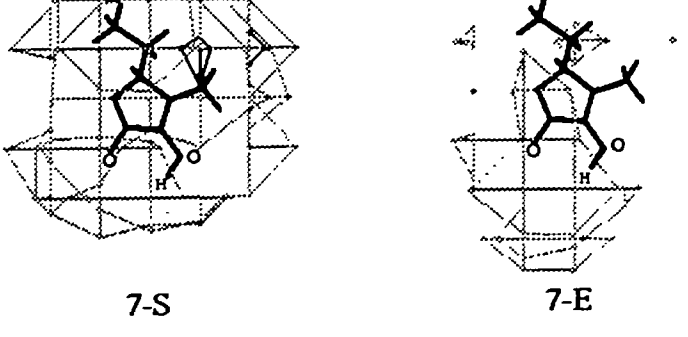

Figure 7 5-ethyl-3-hydroxy-4-methyl-2(5H)-furanone with 3D model for sweet odor. (7-S) Steric information—black contour: steric favored, gray contour: steric unfavored (7-E) Electrostatic information—black contour: negative charge favored; gray contour: negative charge unfavored.

Table 6 Prediction of human olfactory detection threshold values of compounds with sweet odor by 3D model

Compound	Odor description	Data concerning actual threshold values	Calculated threshold values: log (1/threshold value)	Actual threshold values: log (1/threshold value)
2-ethyl-3-hydroxy-4-pyrone	Intensely sweet, fruity-breadlike, pleasant odor of immense tenacity	The manufacturer claims that this material is 4–6 times stronger than its lower homologues	5.9	
cf. 3-hydroxy-2-methyl-4-pyrone (#10, maltol the lower homologue of 2-ethyl-3-hydroxy-4-pyrone)	Sweet, cotton candy, burnt sugar			4.5
5-propenyl-2-ethoxyphenol	Intensely sweet, in the dry state rather medicinal phenolic odor, the sweet odor is more perceptible at high dilution	The manufacturer estimated the power at 25 times that of vanillin	9.5	
cf. 4-hydroxy-3-methoxybenzaldehyde (#8, vanillin)	Intensely sweet, very tenacious creamy-vanilla-like odor			6.7

CoMFA for the QSAR study of odorants

No international standards for evaluation of odor quality and for classification of odor are available. This makes it difficult to advance the QSAR study of odorants. The classification of odorants in this work is not beyond criticism. However, we succeeded in finding a correlation between the steric and electrostatic features of the odorants with human olfactory detection threshold values in two examples (Tables 2 and 5). The r^2 with leave-one-out validation was higher than 0.75 and the r with leave-one-out validation was higher than 0.87 in both examples. The r^2 without validation was higher than 0.95 and the r without validation was higher than 0.98 in both examples. The CoMFA may be useful to analyse other odor qualities.

3D model using CoMFA

The 3D model using CoMFA is considered to be useful, as long as one focuses on the primary odor qualities of odorants. The odorants in this work do not have a simple odor quality as seen in Tables 1, 3, 4 and 6. The threshold data for a sweet odor used for the calculations were measured in different laboratories. Concerning these uncertainties, the prediction in Table 3 is successful to some extent. The ranking of odor strength of the two odorants was successfully predicted in Table 6. If we evaluate the quality of odorants more precisely, measure human olfactory threshold values under the same conditions and increase the number of odorants for the analyses, 3D models for both odor qualities would give a better prediction. In addition, 3D models using CoMFA, as seen in Figures 3 and 6, would help to design new odorants by suggesting the steric and electrostatic requirements.

One 3D model using CoMFA corresponds to one odor quality. The 3D model for sweet odor is not useful to predict the odor strength of the pyrazine derivative with a green odor, though the planar six-membered ring exists in the center of the 3D model for sweet odor. At this point, constructing different 3D models for several important odor qualities using CoMFA would be useful. When we take all odorants, which are said to be about 300 000, into consideration, we need some prediscrimination of odorants by molecular features before applying them to the 3D models using CoMFA.

Assistance to elucidate odorant-receptor interaction

We assume that discrimination of odor qualities in man relates to different combinations of odorant-specific olfactory

receptors. For the two odor qualities in this research, it is not known whether one kind of specific olfactory receptor highly contributes to odor discrimination. However, interaction between odorants with olfactory receptors that contribute to odor discrimination may be deduced from the CoMFA result.

Good correlation between steric and electrostatic features of odorants and human olfactory detection threshold values were found for two odor qualities in this research. Calculated log P values were not necessary to construct the two 3D models. The steric and electrostatic features of odorants are considered to be more important in these two examples. Especially, steric features of odorants seemed important for the interaction with olfactory receptors, because the steric contribution is higher than the electrostatic one as seen in Tables 2 and 5. This suggests that the primary requirements of odorants for interaction with receptors is in the size and shape.

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