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ORIGINAL PAPER

QSAR of α-campholenic derivatives with sandalwood odor, and molecular design

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Abstract Quantitative structure–activity relationship (QSAR) studies have been carried out in a series of α-campholenic derivatives with sandalwood odor based on quantum-chemical data derived by use of the Hartree–Fock (HF) method. To build QSAR models, a multiple linear regression method was used. The models obtained have good predictive ability and are of high statistical significance, with good correlation coefficients, and *p* values less than 0.05. The models contribute also to identification of important quantum-chemical aspects of the sandalwood odor. On the basis of the QSAR models built, several new sandalwood compounds were designed and the best candidate for experimental synthesis was suggested.

Keywords Quantum chemical calculations · Sandalwood · Fragrances · α-Campholenic derivatives · Quantitative structure–activity relationships

Introduction

Olfaction, like other biological processes, involves interaction of a substrate with a receptor site [1]. The nature of the substrate–receptor interaction and the mechanisms of olfaction are not yet completely understood. Odor quality has been related to molecular properties [2–5] or structural elements [6–8]. Generally it is acknowledged that molecular structure and shape have important effect on the specific interaction with the receptor leading to a nerve impulse.

An interesting topic of odor perception is the molecules of sandalwood fragrance. East Indian sandalwood oil, highly prized by perfumers for its fixative properties and characteristic, pleasant, long-lasting, warm, woody, animal-like, milky–nutty scent, is a valuable constituent of perfume compositions. Unfortunately the oil is a scarce perfumery raw material. The growing demand for sandalwood-type odorants, together with the relatively high price and a sometimes sporadic supply of the oil, has stimulated research chemists to search for more accessible and less expensive synthetic substitutes. A large number of substitutes with this typical odor are known already. Among all the diverse substitutes, a series of α-campholenic aldehyde derivatives have attracted much attention and have been the most successful [9]. These compounds have a rigid trimethylcyclopentenyl fragment linked to the osmophoric hydroxyl group by a flexible C4 spacer, similar to (Z)-(−)-β-santalol [10]. Bajgrowicz et al. [11] pointed out that the size, substitution, and possible unsaturation of the spacer decide the intensity, character, and presence of sandalwood odor. In 1998 they synthesized several close analogues of these α-campholenic derivatives by introducing a cyclopropane ring to the structures [12]. Javanol and homo-javanol (Fig. 1, compounds **1**–**8**), are analogues of the above mentioned α-campholenic derivatives in which both C=C bonds are replaced by the isoelectronic cyclopropane rings. It turns out that substituting the alkene double bonds with cyclopropane rings results in increased olfactory power and stability [12]. Some analogues have strong, diffusive, and natural sandalwood-oil scents. Madrol (Fig. 1, compounds **9**, **10**) is

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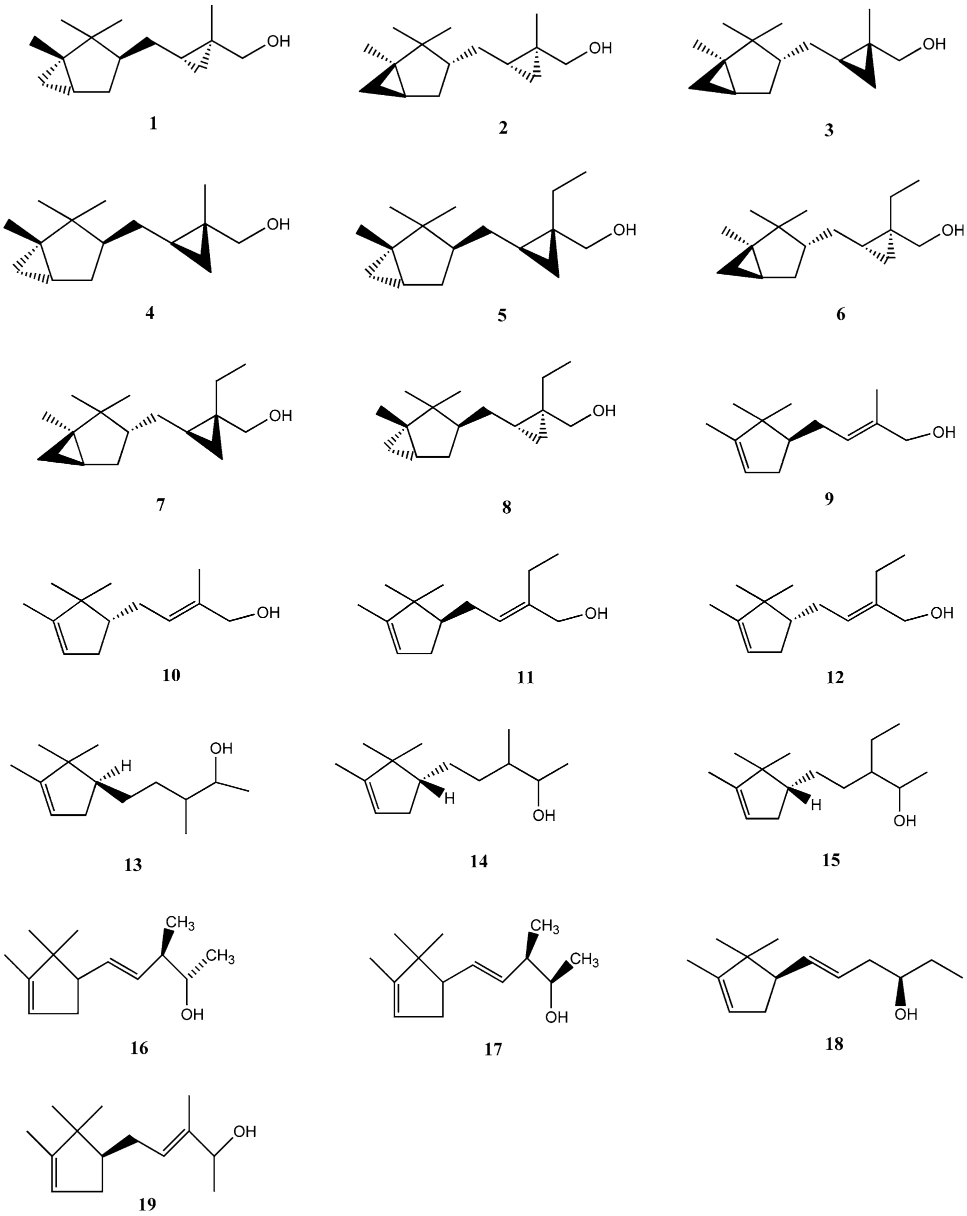

Fig. 1 Geometric structures of the 19 α-campholenic derivatives

another α-campholenic aldehyde derivative with sandalwood odor. Mosandl and Bilke [13] reported that its (*R*)-(+) enantiomer is exclusively responsible for the sandalwood-like odor whereas the (*S*)-(−) enantiomer has only a faint, non-specific odor.

Although the search for the synthetic substitutes has been performed over the last 50 years, little was known about the structure–odor relationship (SOR) of sandalwood-type compounds until very recently. The quantitative structure–activity relationship (QSAR) approach is of great importance in modern chemistry and biochemistry [14]. It has wide application in the development of new molecules for use as drugs, materials, additives, or for other purposes. When a QSAR model between structure and activity is found, one can readily predict the biological activity of untested and sometimes yet unavailable compounds. It is then possible to select the most promising compounds to synthesize and test in the laboratory and reduce experimental research costs greatly. Several QSAR studies have been conducted on sandalwood odor in recent years. Hadaruga et al. [15] performed QSAR studies of a highly diverse set of cycloaliphatic alcohols with sandalwood odor characteristics. The superposition procedure of the MTD method was used to define the probable active conformation. Because of the high diversity of the data set, this method was unable to superimpose all molecules. Consequently, the model built could not be regarded as having very good predictive power. Buchbauer et al. [16] had developed three-dimensional quantitative structure–activity relationship (3D QSAR) models for some synthetic α-campholenic derivatives with sandalwood odor, which do not require spatial alignment of molecules. In their research, both wholistic and substituents descriptors calculated with the TSAR software were used as independent variables. Although the QSAR models obtained from the above two mentioned studies have better predictive ability for sandalwood relative odor intensity, they could not predict exact quantitative sandalwood scent data. Herein we performed QSAR studies of some α-campholenic derivatives based on descriptors derived by the quantum-chemical calculation method. Although approaches based on classical molecular force fields and quantum-chemical methods can both be used for thermodynamic and dipole moment calculations, only quantum-chemical methods are able to provide an accurate and detailed description of the geometric and electronic structures of molecules, for example molecular orbital energies, atomic charges, and many other electronic descriptors of potential value to QSAR studies [14].

Computational methods

All calculations of different quantum-chemical descriptors were performed by use of restricted Hartree–Fock (RHF) theory using the Gaussian 03 program package [17]. The basis set used is the 6-311 + G*, which is the split-valence triple-ξ plus polarization basis set augmented with diffuse functions [18]. Stationary points were characterized as minima without any imaginary vibrational frequency. The structures of 19 α-campholenic aldehyde derivatives selected for QSAR studies are given in Fig. 1. The main criterion for including a compound in the data set is the availability of both qualitative and quantitative data on the sandalwood scent. It should be mentioned that although odor thresholds were published for all eight stereoisomers (**1**–**8**) of javanol and homo-javanol, the thresholds of **4** and **5** are $\geq$15 and >250 ng/dm^3 [11], respectively. Because of the uncertainty of the thresholds, these two isomers could not be involved in the data set when building the model. So 17 were compounds used in the regression process. In this study the odor threshold was used as dependant. *OT* is a measure of odor intensity of a substance. It is defined as the minimum concentration of that substance that can be detected by the human nose. It can be said that the smaller the *OT* value is, the stronger the odor of the molecule. Herein all *OT* values are taken from several publications [11, 12, 16, 19–21]. This paper takes different quantum-chemical descriptors, for example the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), the HOMO–LUMO gap ΔE, the molecular dipole moment μ, the most negative and positive charges on non-hydrogen atoms (q^- and q^+), net charges on the –OH group (q_{OH}), sum of charges of carbon atoms in the cyclopentenyl or cyclopentyl ring (q_{TC}), charges on the C atom neighboring oxygen atom (q_{C}), as independent data. It should be noted that all atomic charges are ESP charges (charges from electrostatic potential fit). All calculated quantum-chemical descriptors and sandalwood odor thresholds are listed in Table 1. The linear regression analyses were executed on a personal computer using the SPSS statistical package (version 11.5; SPSS, Chicago, IL, USA).

Results and discussion

QSAR of α-campholenic derivatives with sandalwood odor

Different combinations of (independent) quantum-chemical data with acceptable correlation with the (dependent) sandalwood activity were used with backward multiple regression analysis to develop meaningful QSAR equations. The equations obtained are of statistical significance with correlation coefficients of approximately 0.8 and *p* values less than 0.05.

$$\begin{aligned}\ln(OT) = {} & 128.367 - 113.682(-0.370)E_{\mathrm{LUMO}}^{-1} \\ & - 2{,}292.384(-2.769)q_{\mathrm{OH}}^{4} + 0.898(0.041)q^{+} \\ & + 58.887(2.290)\ln(q^{-})^{2} + 7.558(0.714)q_{\mathrm{TC}} \\ & + 5.146(1.660)\ln q_{\mathrm{C}}^{2} \end{aligned} \tag{1}$$

$$N = 17,\ R = 0.812,\ R^2 = 0.660,\ R^2_{\mathrm{adj}} = 0.456,$$
$$\mathrm{SE} = 2.451,\ F = 3.231,\ P = 0.049$$

$$\begin{aligned}\ln(OT) = {} & 124.670 - 109.876(-0.358)E_{\mathrm{LUMO}}^{-1} \\ & - 2{,}212.988(-2.673)q_{\mathrm{OH}}^{4} + 56.988(2.216) \\ & \ln(q^{-})^{2} + 7.324(0.692)q_{\mathrm{TC}} + 4.992(1.610)\ln q_{\mathrm{C}}^{2} \end{aligned} \tag{2}$$

$$N = 17,\ R = 0.812,\ R^2 = 0.659,\ R^2_{\mathrm{adj}} = 0.503,$$
$$\mathrm{SE} = 2.341,\ F = 4.243,\ P = 0.021$$

$$\begin{aligned}\ln(OT) = {} & 54.478 - 1{,}879.816(-2.270)q_{\mathrm{OH}}^{4} \\ & + 50.055(1.946)\ln(q^{-})^{2} + 8.923(0.843)q_{\mathrm{TC}} \\ & + 5.473(1.765)\ln q_{\mathrm{C}}^{2} \end{aligned} \tag{3}$$

$$N = 17,\ R = 0.771,\ R^2 = 0.594,\ R^2_{\mathrm{adj}} = 0.459,$$
$$\mathrm{SE} = 2.444,\ F = 4.390,\ P = 0.020$$

Here N is the number of compounds used in the study, R is the correlation coefficient, R^2 is the square of the correlation coefficient, R^2_{adj} is the adjusted R^2 value, *SE* is the standard error, F is the mean square ratio, p is the probability greater than the F value, and values in brackets are standardized coefficients.

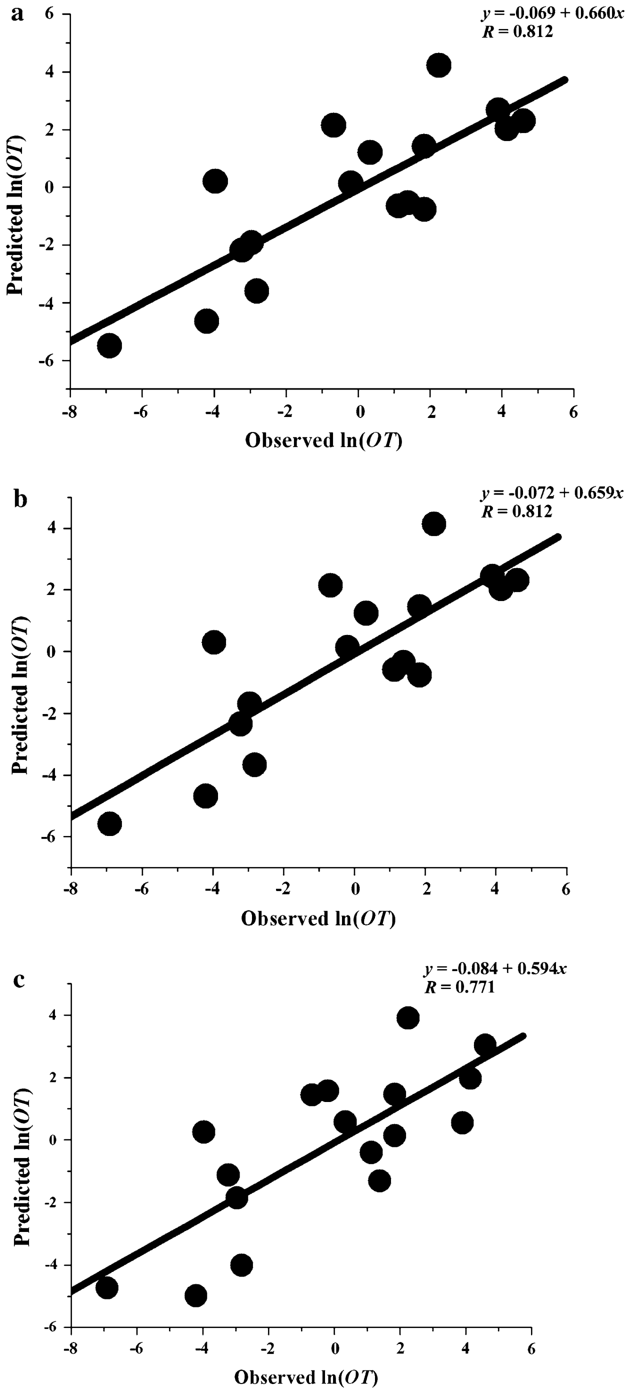

Fig. 2 **a** Predicted ln(*OT*) from Eq. 1 versus observed ln(*OT*). **b** Predicted ln(*OT*) from Eq. 2 versus observed ln(*OT*). **c** Predicted ln(*OT*) from Eq. 3 versus observed ln(*OT*)

These models were used to predict sandalwood odor intensity. According to statistics theory, models were considered to be validated if $R > 0.8$, $R^2 > 0.6$, and $p < 0.05$ between predicted and observed sandalwood activity. It is shown that the three built models except Eq. 3 derived from quantum-chemical descriptors are statistically significant and can be used successfully to predict sandalwood odor activity. The plots of observed ln(*OT*) versus predicted ln(*OT*) are shown in Fig. 2a–c. For any compound, the closer the observed value to the predicted value, the better the predictive ability of the equation. Among these three equations, Fig. 2 shows that Eqs. 1 and 2 have better predictive ability. The observed ln(*OT*), predicted ln(*OT*), and the residuals are presented in Table 2. The relative and mean relative errors between predicted and observed values from Eqs. 1–3 are also shown in Table 2. It can be calculated that the predicted odor threshold (*OT*) errors for some compounds are very small (the error for compound **3** is only 1.269 ng/dm^3) whereas for some compounds the errors are larger (the error for compound **4** is 70.598 ng/dm^3). But, on the whole, the errors from different equations are acceptable. Error analysis indicates that the mean relative error from Eq. 2 is the smallest and thus the values predicted by use of Eq. 2 are closest to the observed values among these three equations. Thus, Eq. 2 seems to be more appropriate for defining odor intensity and was considered to be the best model.

According to statistics theory, if the dimensions of independents are different their standardized coefficients should be used in comparison of their importance to dependence in multiple regression equations. The standardized coefficients in the equations show the importance of some quantum-chemical data, especially q_{OH}, q^{-}, and q_{C}. As shown in Table 1, the values of q_{OH}, q^{-}, and q_{C} are generally between -1 and 1. Accordingly, the more negative q_{OH} is, the smaller the odor threshold and the stronger the sandalwood odor intensity. The equations show that q_{OH} contributes most significantly to explaining the variation in the sandalwood odor intensities among all the data. The more negative q^{-} is, the larger the odor threshold and the weaker the sandalwood odor intensity. The more positive q_{C} is, the larger the odor threshold and the weaker the sandalwood odor intensity. According to classical chemical theory, all chemical interactions are, by nature, either electrostatic (polar) or orbital (covalent). Electrical charges in the molecule are obviously the driving force of electrostatic interactions [14]. The involvement of net charges on the –OH group (q_{OH}), the most negative charge on non-hydrogen atoms (q^{-}), and net charges on the C atom neighboring the oxygen atom (q_{C}), suggests that the –OH group, the non-hydrogen atom-populated most negative charge, and the C atom neighboring oxygen atom are the sites of odor activation. Olfaction is regarded as a bimolecular process involving the interaction of an airborne molecule with a complementary site of a receptor system in the brain. It is well known that, in many cases, compounds with totally different structures produce the same odor. This is because these compounds interact with receptors to create similar sensory impressions in the

Table 1 Sandalwood odor thresholds (*OT*) and calculated quantum-chemical data at the HF/6-311 + G* level

Comp.	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	μ (Debye)	q_{OH} (a.u.)	q^{+} (a.u.)	q^{-} (a.u.)	q_{TC} (a.u.)	q_{C} (a.u.)	*OT* (ng/dm^3)
1	−8.7089	1.6842	10.3931	1.4116	−0.2808	0.7970	−0.7604	0.7016	0.08794	0.015
2	−10.1880	1.7204	11.9084	1.5647	−0.2942	0.5264	−0.7688	0.7288	0.1741	0.510
3	−10.2082	1.7180	11.9262	1.7857	−0.2929	0.5229	−0.7659	0.7286	0.1628	1.400
6	−10.1929	1.7011	11.8940	1.6517	−0.2835	0.5126	−0.7344	0.7613	0.2495	99.000
7	−10.2177	1.7005	11.9182	1.8680	−0.2646	0.5495	−0.7178	0.7735	0.1703	3.100
8	−8.7203	1.6712	10.3915	1.4804	−0.2569	0.8682	−0.7102	0.7784	0.1596	0.040
9	−8.9409	1.6888	10.6297	1.5283	−0.2683	0.8093	−0.7232	0.0043	0.2246	0.060
10	−8.9828	1.7209	10.7037	1.4613	−0.2798	0.4159	−0.7324	0.2272	0.2515	4.000
11	−8.9186	1.6837	10.6023	1.5877	−0.2550	0.9089	−0.6742	−0.0643	0.3587	0.001
12	−8.9975	1.7215	10.7190	1.4848	−0.2693	0.4290	−0.6900	0.1657	0.3737	0.052
13	−8.9344	1.7177	10.6521	1.8761	−0.3534	0.7074	−0.8372	0.1277	0.4658	6.325
14	−8.9442	1.7340	10.6782	1.6278	−0.3382	0.5762	−0.8071	0.1515	0.4674	6.325
15	−8.9425	1.7471	10.6896	1.6095	−0.3448	0.5946	−0.8135	0.1571	0.5431	63.25
16	−8.9523	1.7533	10.7056	1.8741	−0.3533	0.5674	−0.8258	0.1834	0.5082	0.019
17	−8.9396	1.7253	10.6649	1.6919	−0.3176	0.6008	−0.7854	0.2215	0.4295	9.500
18	−8.8193	1.7952	10.6145	1.6609	−0.3245	0.8245	−0.7610	0.1453	0.5258	49.500
19	−8.9366	1.6693	10.6059	1.5162	−0.3272	0.6491	−0.8127	0.0626	0.3608	0.820

Table 2 Observed and predicted ln(*OT*) values, residuals of the investigated compounds, relative errors (%), and mean relative errors (%) between observed and predicted values

	Obs.[a]	Pre.[b]	Res.[b]	Rela. Err.[b]	Pre.[c]	Res.[c]	Rela. Err.[c]	Pre.[d]	Res.[d]	Rela. Err.[d]
1	−4.200	−4.652	−0.453	10.8	−4.686	−0.487	11.6	−4.986	−0.786	18.7
2	−0.673	2.141	2.815	418.1	2.146	2.819	418.6	1.445	2.118	314.6
3	0.336	1.207	0.871	258.8	1.242	0.905	269.1	0.574	0.238	70.7
6	4.595	2.299	−2.296	50.0	2.314	−2.281	49.6	3.027	−1.568	34.1
7	1.131	−0.647	−1.778	157.1	−0.586	−1.718	151.8	−0.401	−1.532	135.4
8	−3.219	−2.179	1.040	32.3	−2.349	0.870	27.0	−1.118	2.101	65.3
9	−2.813	−3.601	−0.788	28.0	−3.670	−0.857	30.5	−4.011	−1.197	42.6
10	1.386	−0.539	−1.925	138.9	−0.356	−1.742	125.7	−1.304	−2.690	194.1
11	−6.908	−5.501	1.407	20.4	−5.590	1.318	19.1	−4.736	2.171	31.4
12	−2.957	−1.922	1.034	35.0	−1.702	1.254	42.4	−1.853	1.104	37.3
13	1.845	−0.766	−2.611	141.6	−0.764	−2.609	141.4	0.141	−1.703	92.4
14	1.845	1.417	−0.428	23.2	1.448	−0.396	21.5	1.462	−0.382	20.7
15	4.147	2.035	−2.112	50.9	2.040	−2.107	50.8	1.972	−2.175	52.4
16	−3.963	0.200	4.163	105.0	0.294	4.257	107.4	0.256	4.220	106.5
17	2.251	4.228	1.977	87.8	4.131	1.880	83.5	3.903	1.652	73.4
18	3.902	2.675	−1.227	31.4	2.440	−1.462	37.5	0.549	−3.353	85.9
19	−0.198	0.133	0.332	167.2	0.130	0.329	165.7	1.573	1.771	892.6
Mean Rela. Err.		–	–	103.3	–	–	103.1	–	–	133.4

[a] The observed values were measured and evaluated by the GC–sniffing technique

[b] Predicted ln(*OT*), residuals and relative errors calculated by use of Eq. 1

[c] Predicted ln(*OT*), residuals and relative errors calculated by use of Eq. 2

[d] Predicted ln(*OT*), residuals and relative errors calculated by use of Eq. 3

sensory centers of the brain. It is the active sites of compounds that make the interaction with receptors possible. So the active sites of odorants are of critical importance. On the other hand, odorant molecules usually contain both a strong hydrophobic and a relatively weak polar region. The latter, usually termed the “osmophore”, is associated

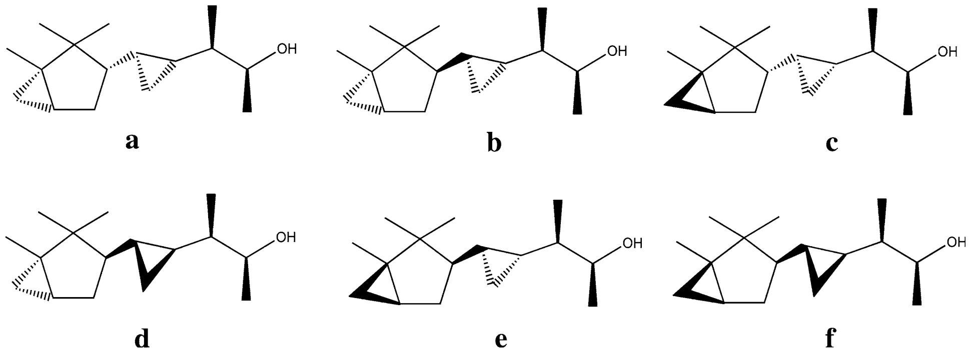

Fig. 3 Geometric structures of various new molecules

Table 3 Total energies (*E*), zero-point energies (ZPE), and relative energies (RE) for new molecules

Species	HF/6-311 + G*		
	E (Hartree)	ZPE (kJ/mol)	RE (kJ/mol)
a	−697.11575	1,150.3 (0)[a]	17.6
b	−697.10894	1,149.8 (0)	35.0
c	−697.12197	1,149.0 (0)	0.0
d	−697.10894	1,149.8 (0)	35.0
e	−697.10659	1,150.2 (0)	41.6
f	−697.10894	1,149.8 (0)	35.0

[a] The integers in parentheses are the number of imaginary frequencies (NIMAG)

with a functional group such as hydroxyl, carbonyl, occasionally ether, or a limited variety of heteroatomic homologues. The significant importance of the –OH group is also embodied in the built equations. In addition, from the regression equations one can see that although the energy of the lowest unoccupied molecular orbital (E_{LUMO}) and sum of charges of carbon atoms in the cyclopentenyl or cyclopentyl ring (q_{TC}) do not contribute significantly to explaining sandalwood odor activity of molecules, their effects on odor intensity could not be neglected. The lower the E_{LUMO}, the smaller the odor threshold and the stronger the sandalwood odor intensity. According to the frontier molecular orbital theory (FMO) of chemical reactivity, $\mathrm{E}_{\mathrm{LUMO}}$ is directly related to the electron affinity. The lower the $\mathrm{E}_{\mathrm{LUMO}}$ value, the stronger the ability of the molecule to accept electrons. Accordingly, we predict sandalwood compounds seem to act as electron acceptors in the creation of sensory impressions. The equations show that the smaller q_{TC} is, the smaller the odor threshold and the stronger the sandalwood odor intensity. Regarding this phenomenon, we feel regret that there seems no obvious reason to explain it at present.

Molecular design of new sandalwood compounds

On the basis of the idea that substituting the alkene double bonds with the cyclopropane rings in α-campholenic derivatives may create increased olfactory power and stability [12], we have designed several new molecules. The structures of compounds **a**–**f** are shown in Fig. 3. The total energies, zero-point energies (ZPE), relative energies (with ZPE corrections), and number of imaginary frequencies are listed in Table 3. Harmonic vibrational frequency calculations indicate that all isomers **a**–**f** are local minima on their potential energy surfaces at the HF level of theory. As listed in Table 3, the same total energies and zero-point energies (ZPE) of isomers **b**, **d**, and **f** indicate that these three isomers have the same conformation after optimization. Further analysis shows that the isomers **b** and **d** are unstable and they convert to conformation **f** during the optimization process. To predict the odor intensities of this series of compounds, we calculated their various quantum-chemical data; the corresponding results are listed in Table 4. In addition, because the data for **b**, **d**, and **f** are same, only **f** is included in Table 4. The ln(*OT*) values were the predicted by substituting the calculated quantum data into Eqs. 1–3. The results show that the odor threshold values of these compounds are all less than 1.370 ng/dm^3, indicative of their strong odor. Isomer **c** is the most

Table 4 The quantum-chemical data calculated for various new molecules

Species	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	μ (Debye)	q_{OH} (a.u.)	q^{+} (a.u.)	q^{-} (a.u.)	q_{TC} (a.u.)	q_{C} (a.u.)
a	−10.2471	1.6206	11.8676	1.5769	−0.3714	0.5988	−0.8478	0.5077	0.4872
c	−10.2520	1.6616	11.9136	1.7405	−0.3772	0.5045	−0.8647	0.3775	0.4596
e	−10.0455	1.6606	11.7061	1.5285	−0.3924	0.6513	−0.8783	0.2653	0.5001
f	−10.0537	1.6758	11.7295	1.4448	−0.3665	0.5934	−0.8494	0.5812	0.4355

energetically favored. So we predict isomer **c** should be regarded as the best candidate for experimental synthesis.

Summary

The objective of this study was to develop a QSAR model for prediction of the odor intensities of some α-campholenic derivatives. The model can be used for the design and discovery of new compounds with sandalwood odor. It was shown that compounds which have identical chemical structures but differ only in the configuration of their chiral centers and, consequently, in their biological activity, can be described and distinguished by descriptors of the entire molecule and its substituents. The model contributes also to the identification of important quantum-chemical data responsible for sandalwood odor. However, because of poor availability of accurate odor threshold data on sandalwood scent, we regret that only 17 α-campholenic derivatives are involved in this study. In future, we will make a collection of more related data to continuously refine our model. Based on the QSAR models built, we have designed several new sandalwood compounds and suggested the best candidate for experimental synthesis. We hope our research may provide a basis for the development of new sandalwood products.

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