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ORIGINAL PAPER

# Study of the structural and electronic origin of the sandalwood odor of some terpenylcyclohexanols

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**Abstract** The correlation between structural and electronic features and the sandalwood odor of some terpenylcyclohexanols is established on the basis of quantum chemical calculation methods. A definite structural fragment with electronic properties determining the origin of the odor is revealed. The effects of HOMO–LUMO energy gaps and total energies of some terpenylcyclohexanols on their odor intensity are investigated.

**Keywords** Quantum chemical calculations · Electronic structure · Fragrances · Structure–activity relationships

## Introduction

Olfaction, like other biological processes, involves interaction of a substrate with a receptor site. The nature of the substrate–receptor interaction and how this interaction leads to a perceived odor has yet to be elucidated [1]. Many theories have been proposed to explain the molecular basis of odor perception considering mainly molecular properties [2–5] or structural elements [6–8]. References about the structure of the receptor few in number [9], and from these no general conclusion about the site of the receptor system has been drawn. Generally it is acknowledged that the structures of odor molecules have major effects on the specific interaction with the receptor leading to nerve impulses.

An interesting topic for research on odor perception is the molecules of sandalwood fragrance. East Indian sandalwood oil, highly prized by perfumers for its fixative properties and persistent, heavy, sweet, woody scent, mainly consists of the closely related sesquiterpenoids $\alpha$-santalol and $\beta$-santalol [10]. The santalols, which account for up to 90% of the oil, are generally considered to be responsible for the main odor character. 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 cheaper synthetic substitutes. Careful examination of the substitutes soon raised questions about which structural features were required for a compound to have sandalwood-type odor activity. Consequently, a substantial amount of research work [5, 11–15] has been carried out on structure–activity relationships (SAR) in this odor area. Buchbauer et al. [5] have performed conformational calculations on two relatively rigid molecules with sandalwood odor by molecular mechanics and the semiempirical method AM1. Comparison of geometries shows that a common structural element exists in the relative arrangement of a carbinol function and a quaternary carbon atom. Both enantiomers of *tert*-butylbicyclo[4.4.0]decan-3-ol, a sandalwood odorant, used as standard for molecular calculations on the group of sandalwood fragrance molecules, were separated and analyzed [14]. The results show that sandalwood odor is highly sensitive to the chiroptical properties of the molecules. Dimoglo et al. [15] investigated the relationship between the sandalwood odor and structure of some alcohols by an electron-topological method. The investigation led to identification of an activity fragment

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which is present in all active molecules but absent from the inactive ones. The activity fragment contains two adjacent carbon atoms, $C_i$ and $C_j$, one hydroxyl group, and three neighboring carbon atoms ($C_k$, $C_l$, $C_m$), where $C_i$, $C_j$, $C_k$ are quaternary or tertiary in nature and small positive charges reside on the $C_i$ and $C_j$ atoms. The distances from the hydroxyl group to $C_i$ and $C_j$ were estimated to be 6.4–6.8 and 7.4–7.8 Å. In the paper Dimoglo suggested that $C_i$ and $C_j$ form an electron-donor center and that $C_k$, $C_l$, and the hydroxyl group an electron-acceptor center.

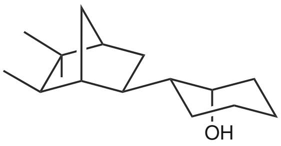
As mentioned above, there are many publications on the relationship between chemical structure and sandalwood odor. However, it is noticeable that whatever odor "rules" are deduced, there are always exceptions [12]. So there is a need to find new, more correct rules which relate chemical structure to sandalwood odor. In this paper we present the results of a study, based on quantum chemical calculation methods, of structural and electronic features of some terpenylcyclohexanols with sandalwood odor. The method used made it possible to achieve the clearest and most complete isolation of the structural fragment with definite geometric and electronic properties responsible for sandalwood odor.

## Results and discussion

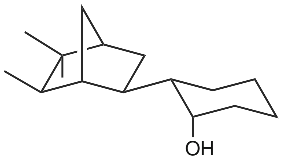
Of the synthetic sandalwood odorants, the first commercially successful material resulted from chance discovery. It is a mixture of isomeric terpenylcyclohexanols synthesized by reaction of either phenol or guaiacol with camphene followed by catalytic hydrogenation [16]. It has been pointed out that the odor intensity of these isomers is quite different, depending on the position of the hydroxyl group at the cyclohexane ring. Figure 1 shows the structures of all the isomers investigated (**1**–**9**), Table 1 lists the corresponding fragrance activity.

As shown in Table 1, only two of the isomers, **3** and **4**, have a pronounced sandalwood odor, one isomer, **5**, has an odor resembling that fragrance, two isomers, **8** and **9**, have weak sandalwood odor, and for all the other compounds (**1**, **2**, **6**, **7**) this activity is lacking [17]. Different methods have been used in attempts to explain this variation [5, 11]. The optimized structures of all the isomers are displayed in Fig. 2.

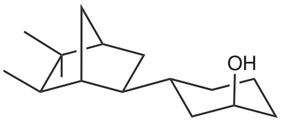
As Bersuker et al. [18] suggested, analysis based on structural and stereochemical features only (bond lengths and angles, distances between specific atomic groups, etc.) is not enough to establish the features from which the odor originates. Electronic structure analysis, for example the atomic contribution to the highest occupied molecular orbital (HOMO) or lowest unoccupied molecular orbital (LUMO), is therefore introduced in this paper to reveal



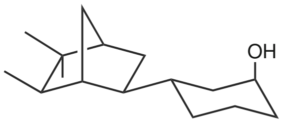
**1** odorless



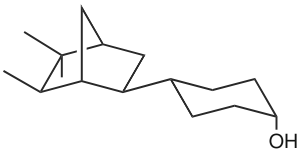
**2** odorless



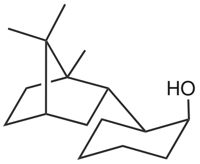
**3** strong



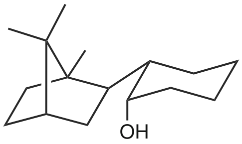
**4** strong



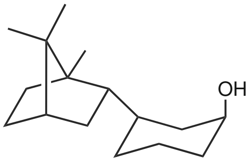
**5** resemblance



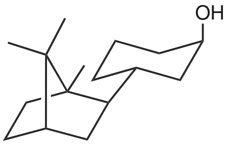
**6** odorless



**7** odorless



**8** weak

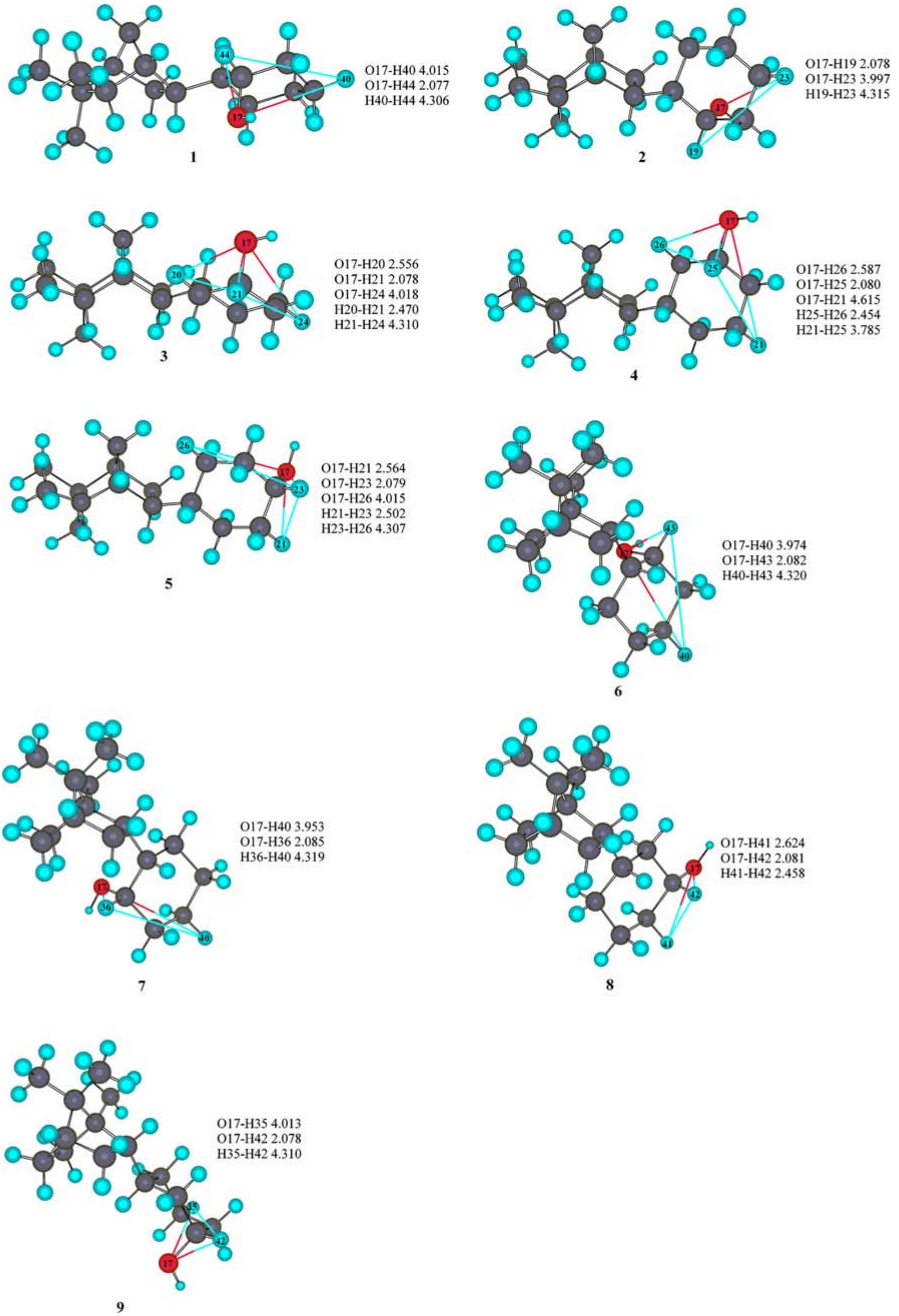


**9** weak

**Fig. 1** The geometric isomers of the various terpenylcyclohexanols

**Table 1** Fragrance of the various terpenylcyclohexanols

| Isomer | Fragrance |
|---|---|
| **1** | No sandalwood odor |
| **2** | No sandalwood odor |
| **3** | Strong sandalwood odor |
| **4** | Strong sandalwood odor |
| **5** | Resemblance to sandalwood odor |
| **6** | No sandalwood odor |
| **7** | No sandalwood odor |
| **8** | Weak sandalwood odor |
| **9** | Weak sandalwood odor |



1
O17-H40 4.015
O17-H44 2.077
H40-H44 4.306

2
O17-H19 2.078
O17-H23 3.997
H19-H23 4.315

3
O17-H20 2.556
O17-H21 2.078
O17-H24 4.018
H20-H21 2.470
H21-H24 4.310

4
O17-H26 2.587
O17-H25 2.080
O17-H21 4.615
H25-H26 2.454
H21-H25 3.785

5
O17-H21 2.564
O17-H23 2.079
O17-H26 4.015
H21-H23 2.502
H23-H26 4.307

6
O17-H40 3.974
O17-H43 2.082
H40-H43 4.320

7
O17-H40 3.953
O17-H36 2.085
H36-H40 4.319

8
O17-H41 2.624
O17-H42 2.081
H41-H42 2.458

9
O17-H35 4.013
O17-H42 2.078
H35-H42 4.310

**Fig. 2** The optimized structures of all the molecules investigated, and the layout of the activity fragment

**Table 2** Electronic characteristics of the activity fragment

| Isomer | Mulliken charges on atoms | | | | $C_K^a$ of 1s AOs | | |
|---|---|---|---|---|---|---|---|
| | O | $H_i$ | $H_j$ | $H_k$ | $H_i$ | $H_j$ | $H_k$ |
| **1** | −0.63 | 0.11 | 0.11 | 0.13 | 0.28 | 0.01 | −0.12 |
| **2** | −0.63 | 0.10 | 0.11 | 0.13 | −0.22 | −0.00 | 0.12 |
| **3** | −0.63 | 0.11 | 0.15 | 0.13 | −0.29 | 0.10 | 0.13 |
| **4** | −0.63 | 0.10 | 0.15 | 0.13 | 0.24 | −0.12 | −0.15 |
| **5** | −0.63 | 0.11 | 0.14 | 0.13 | 0.28 | −0.11 | −0.13 |
| **6** | −0.62 | 0.11 | 0.12 | 0.13 | −0.24 | −0.02 | 0.13 |
| **7** | −0.62 | 0.11 | 0.12 | 0.13 | −0.27 | −0.03 | 0.12 |
| **8** | −0.63 | 0.10 | 0.14 | 0.12 | 0.21 | −0.11 | 0.05 |
| **9** | −0.63 | 0.11 | 0.15 | 0.13 | 0.230 | −0.09 | −0.12 |

[a] Here $C_K$ is the coefficient of the respective AO in the HOMO

**Table 3** The calculated HOMO and LUMO energies, HOMO–LUMO energy gaps, and odor intensity of the molecules investigated

| Isomer | HOMO (Hartree) | LUMO (Hartree) | $\Delta E$ (kJ mol$^{-1}$) | Odor intensity |
|---|---|---|---|---|
| **1** | −0.25574 | 0.06473 | 841.4 | Odorless |
| **2** | −0.25617 | 0.06481 | 842.7 | Odorless |
| **3** | −0.25629 | 0.06862 | 853.1 | Strong |
| **4** | −0.25658 | 0.07442 | 869.0 | Strong |
| **5** | −0.25687 | 0.06750 | 851.6 | Resemblance[a] |
| **6** | −0.25963 | 0.05992 | 839.0 | Odorless |
| **7** | −0.26048 | 0.05848 | 837.4 | Odorless |
| **8** | −0.25487 | 0.06569 | 841.6 | Weak |
| **9** | −0.25577 | 0.06630 | 845.6 | Weak |

[a] The fragrance of isomer **5** resembles that of sandalwood

combined electronic, structural, and stereochemical features responsible for the sandalwood odor.

Geometry optimization and electronic structure analysis revealed that all active sandalwood compounds (**3**, **4**, and **5**) possess an activity fragment which is absent from the inactive compounds. The electronic characteristics of the activity fragment are presented in Table 2. The layout of the activity fragment is shown in the corresponding optimized structures of isomers **3**, **4**, and **5** (Fig. 2). As shown in Fig. 2, the activity fragment consists of one oxygen and three hydrogen atoms. Of the three hydrogen atoms, the first is bonded to the carbon atom adjacent to the oxygen atom (this H atom is named $H_i$); the second is bonded to the carbon atom which is separated from the oxygen by two carbon atoms (this H atom is named $H_j$); the third is bonded to the carbon atom which is separated from the oxygen by three carbon atoms (this H atom is named $H_k$). The O–$H_i$, O–$H_j$, and O–$H_k$ distances were estimated to be approximately 2.1, 2.6, and 4.0–4.7 Å. It should also be noted that atoms $H_j$ and $H_k$ are on two sides of the C–O bond. There are several rules these atoms must obey in addition to the spatial requirements. As shown in Table 2, the four atoms must make a major contribution to the HOMO of the molecule or to an occupied orbital lying close to the HOMO; the signs of the LCAO coefficients ($C_K$) of the 1s functions of $H_j$ and $H_k$ should coincide; the signs of the LCAO coefficients ($C_K$) of the 1s functions of $H_i$ should be different from those for $H_j$ and $H_k$; the negative charge of the oxygen atom is −0.63; the charges on the three hydrogen atoms are all positive and vary from 0.10 to 0.15. For other weak and inactive isomers (**1**, **2**, **6**, **7**, **8**, **9**), the atomic contributions to the HOMO were also investigated. From a spatial viewpoint, the four atoms O, $H_i$, $H_j$, and $H_k$ all exist in these isomers (Fig. 2). But for each inactive isomer (**1**, **2**, **6**, **7**), as shown in Table 2, among the three hydrogen atoms, there is one ($H_j$ or $H_k$) whose LCAO coefficient of the 1 s functions ($C_K$) is so small ($\leq 0.03$) that its contribution to the HOMO of the molecule may be neglected. This is to say, there are only three atoms (one oxygen and two hydrogen atoms) which make major contributions to the HOMO of the molecule, which is different from the active molecules. For the other two weak sandalwood isomers (**8** and **9**), although the LCAO coefficients of the 1s functions ($C_K$) of $H_k$ in isomer **8** and of $H_j$ in isomer **9** are still less than 0.1, they can be regarded as making a minor contribution to the HOMO. So it seems reasonable that these two isomers have weak sandalwood odor.

To further investigate the effect of the frontier molecular orbital (FMO) on the odor intensity of the odorant molecules, we computed the HOMO–LUMO energy gaps of all the isomers investigated. The corresponding results are listed in Table 3. Compared with the experimental results, we found isomers with strong odor generally have larger HOMO–LUMO energy gaps. Because the FMO is a molecule's activity region, it seems that the occurrence of such a phenomenon is not fortuitous. The total energies, zero-point vibrational energies, and relative energies of all the active and inactive molecules investigated are listed in Table 4; these show there is no positive connection between odor intensity and an isomer's total energy. That is to say, it is not certain that the lower the energy is, the stronger the odor of the isomer. This result is consistent with that of Gorbachov and Rossiter [19]. For example, isomer **1** is 3.8 kJ mol$^{-1}$ lower in energy than **4**, whereas **1** is odorless and **4** is strong in odor. Moreover, Table 4 shows that all the isomers investigated are close in energy, but their fragrances are diverse.

**Table 4** Total energy (*E*), zero-point energy (*ZPE*), relative energy (*RE*), and odor intensity of the various isomers

| B3LYP/6-31G* | | | | |
|---|---|---|---|---|
| Isomer | *E* (Hartree) | *ZPE* (kJ mol$^{-1}$) | *RE* (kJ mol$^{-1}$) | Odor intensity |
| **1** | −701.78877 | 1098.3 (0)[a] | 0.0 | Odorless |
| **2** | −701.78529 | 1098.7 (0) | 9.6 | Odorless |
| **3** | −701.78928 | 1097.9 (0) | 1.7 | Strong |
| **4** | −701.78739 | 1098.3 (0) | 3.8 | Strong |
| **5** | −701.78701 | 1099.1 (0) | 5.4 | Resemblance |
| **6** | −701.77815 | 1098.7 (0) | 28.5 | Odorless |
| **7** | −701.77837 | 1098.7 (0) | 27.6 | Odorless |
| **8** | −701.78019 | 1098.3 (0) | 22.6 | Weak |
| **9** | −701.78610 | 1098.3 (0) | 7.1 | Weak |

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

## Conclusion

This paper reports an investigation of the structural and electronic properties of some terpenylcyclohexanols. Geometry optimization and electronic structure analysis revealed that all active sandalwood compounds have an activity fragment which is absent from the inactive compounds. The activity fragment consists of one oxygen and three hydrogen atoms. The four atoms must make a major contribution to the HOMO of the molecule or to an occupied orbital lying close to the HOMO; the signs of the LCAO coefficients of the 1s functions of $H_j$ and $H_k$ should coincide; the signs of the LCAO coefficients of the 1s functions of $H_i$ should be different from those of $H_j$ and $H_k$; the negative charge of the oxygen atom is −0.63; the charges on the three hydrogen atoms are all positive and vary from 0.10 to 0.15. The O–$H_i$, O–$H_j$, and O–$H_k$ distances were estimated to be approximately 2.1, 2.6 and 4.0–4.7 Å. We also found that isomers with strong odor generally have larger HOMO–LUMO energy gaps. There is no positive connection between odor intensity and an isomer's total energy.

## Computational methods

All calculations were performed using the Gaussian 03 program package [20]. We optimized geometries and calculated the harmonic vibrational frequencies for some terpenylcyclohexanols at the B3LYP/6-31G* level of theory, where B3LYP is the DFT method using Becke's three-parameter gradient-corrected functional [21] with the gradient-corrected correlation of Lee et al. [22], and 6-31G* is the split-valence double-$\zeta$ plus polarization basis set [23]. Stationary points were characterized as minima without any imaginary vibrational frequency and a transition state with only one imaginary vibrational frequency. Based on the optimized geometries, we have calculated the frontier orbital energies and performed frontier molecular orbital (FMO) analysis to understand the atomic contribution.

Throughout this paper, bond lengths are given in ångströms, total energies, and HOMO and LUMO energies in Hartrees, and HOMO–LUMO energy gaps, and relative and zero-point vibrational energies in kJ mol$^{-1}$.

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