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ORIGINAL PAPER

Study of structural and electronic origin of ambergris odor of some compounds

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Abstract The correlation between structural, stereochemical as well as electronic features and ambergris odor of some tricyclic ethers is established based on quantum chemical calculation method. A definite structural fragment (a "new ambergris triangle") with certain electronic properties determining the origin of the odor is revealed. The influence of HOMO-LUMO energy gaps and total energies of some ambergris compounds on their odor intensity is investigated.

Keywords Ambergris · Frontier molecular orbital (FMO) · HOMO · Odor intensity

Introduction

Since ancient times, spices and resins from animal and plant sources have been used extensively for perfumery and flavor purposes. Ambergris has been one of the most highly valued perfumery materials of animal origin. It is a secretion found in the intestinal tract of the sperm whale and when released into the sea takes the form of lumps which are rarely more than 20 cm in diameter [1]. When first formed, the material is dark brown to black in color, but after several years of aging, as a result of the action of sunlight, air and sea water, the material gradually fades to a light grey or creamy yellow color. At the same time, the main component, the odorless triterpene alcohol ambrein (**1**, Fig. 1) is oxidatively degraded. Some of the products resulting from this chemical process are responsible for the organoleptic properties of ambergris: among the first to be identified were the tricyclic ether **2** and its hydrogenated analogue **3** [2]. The related tricyclic ethers **5** and **6** were prepared during an investigation of the oxidation products from the labdane diterpenoid (-)-sclareol (**4**) [3, 4]. Compound **5** known as Ambrox, has become a key ambergris-type fragrance used in perfumery and was only later, in 1977, identified among the odoriferous constituents of tincture of ambergris [5].

Ambergris has been used for many years in the perfume and medical industries to fix the odors of scents. However, in the 20th Century, the growing demand for ambergris-type odorants, coupled to the dwindling of natural sources, has stimulated the search for more accessible and cheaper substitutes. A large number of analogues of **5** and **3** have been prepared and characterized [2]. The careful examination of these analogues soon raised the question as to which structural features were required for a compound to have an ambergris-type odor activity. Consequently, a considerable amount of research work [6–9] has been carried out on structure-activity relationships (SAR) in this odor area, and the corresponding theories that are taken seriously can be grouped into two classes, i.e., recognition and vibration [10]. Both classes propose that an odorant molecule comes into contact with a receptor causing the cell containing the receptor to generate a nerve impulse. In the recognition theories, contact is due to molecular recognition of a substrate (the odorant) by a protein (receptor); while in the vibration theory, the receptor in some way senses a specific molecular vibration or group of vibrations in the substrate.

Two recognition theories deserve to be especially mentioned. The first is that of Ohloff [6]. After studying a large number of analogues of natural ambergris compo-

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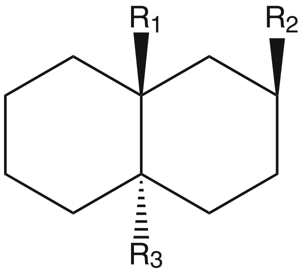
nents, Ohloff formulated a “triaxial rule” in 1971. It states that ambergris-type odors are inherent to substances with a trans-decalin carbon skeleton and three axial substituents (R1, R2, and R3) arranged as indicated in structure (**I**),

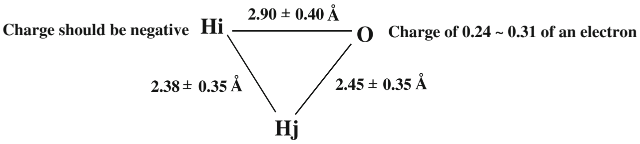


I

one of the substituents Ri being an oxygen-containing functional group (or such a group being located at one of the carbon atoms bonded to the radicals Ri).

However, there are a few cis-decalins (e.g., compound (**5**), Fig. 1), and the number of ambergris odorants which do not even contain a decalin system smell of ambergris. Examples include Timberol (**12**) [11], 4-isopropenyl-1,3,3,5, 5-pentamethylcyclohexanol(**13**) [12], Karanal (**14**) [13], cyclohexyltetrahydrofuran (**15**) (Fig. 2) [14]. Conversely, a series of compounds (see [3, 4]) which satisfy the requirements of the “triaxial rule”, are odorless. Thus, Ohloff’s “triaxial rule” is clearly incomplete.

The second is the electronic-topological method. In 1983 Vlad and co-workers discovered a new type of ambergris odorant, the cyclohexyltetrahydrofuran (**15**) [14]. The absence of a decalin ring system in this compound presumably inspired Vlad’s group to look for an alternative structure-ambergris odor relationship. In this theory, recognition involves the electrons of the frontier orbitals of the odorant and presupposes a series of so-called “ambergris triangle” [15]. They claimed that ambergris odorants all contain an “ambergris triangle” (see structure II)



II Vlad's "ambergris triangle"

of certain dimensions formed by an oxygen atom and two hydrogen atoms, which interact electronically with the postulated amber receptor. There are several rules which these atoms must obey in addition to the spatial requirements. The three atoms must make a major contribution to the LUMO of the molecule, or to an unoccupied orbital lying close to the LUMO; the signs of the LCAO coefficients of the two hydrogen 1 s functions should coincide, which means that the electron distribution in the space between these atoms is bonding; the negative charge of the oxygen atom varies from −0.24 to −0.31 electron; the charge on the most distant (to the oxygen) hydrogen is always negative and the charge density over the triangle should be $-0.1e/Å^2$. However, the negative charge on the hydrogen atom (H_i) furthest away from the oxygen atom seems questionable. Furthermore, the ring opened material does not seem to have been included in the list of structures which they studied.

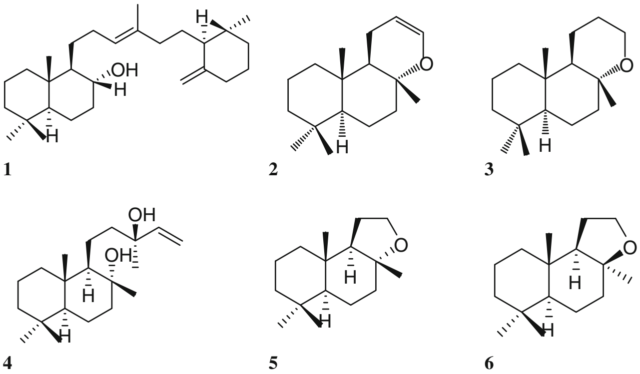


Fig. 1 Some ambergris odorants and their natural precursors

Vibration theory is an old idea, first proposed by Dyson [16] in 1937 and later extended by Wright [17] in the 1950s and 1960s. They proposed that a receptor in the nose detects the vibrations of odorant molecules, which the brain interprets as odors. Nevertheless, one of the weaknesses of their theory was that it could not explain how a receptor might sense vibration. Such a mechanism has now been provided by Turin [18]. He proposes the presence of an electric potential gap in the receptor proteins, with NADPH and zinc ions providing the “electrodes”. Electrons cannot cross the gap unless an odorant molecule is placed between these electrodes. In order to cross the gap the electrons must lose energy, which they do by tunneling through the orbitals of the odorant molecule and exciting vibrational modes in it as a result. Thus Turin has moved the search for correlations from infrared to inelastic electron tunneling spectra.

Based on the above introduction, there is a need to find new, more correct rules which relate the chemical structure and ambergris odor. In this paper, we shall present the results of a study of structural, stereochemical and electronic features of some typical ambergris odorant molecules based on quantum chemical calculation method. Such a method made it possible to achieve the clearest and most complete isolation of the structural fragment with definite geometric and electronic properties responsible for ambergris odor.

Molecule’s odor is influenced by many factors, such as structural and stereochemical features, functional groups, and electronic properties etc. Nevertheless, many inves-

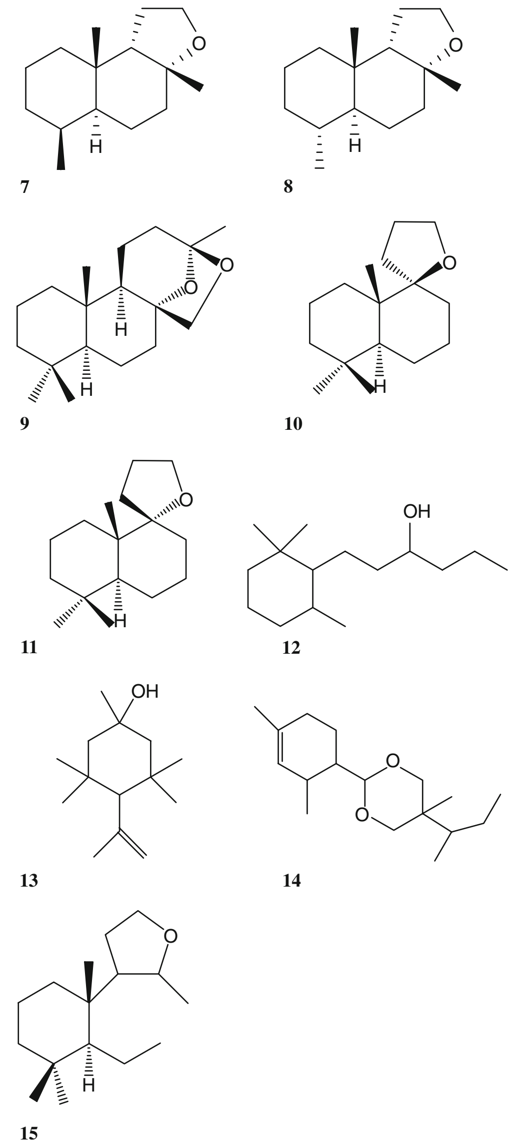
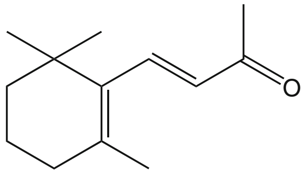
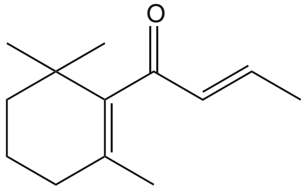


Fig. 2 Some typical ambergris-type odor compounds

tigations [15, 19] show that no single molecular property is sufficient to determine the odor of a molecule. Odor quality is multidimensional, but it is evident that odor is exclusively associated with volatile molecules. The highest molecular weight found so far for an odorant is 294 [20]. Olfaction is considered to be a bimolecular process involving the interaction of an airborne molecule with a complementary site of a receptor system. It is well known that, in many cases, compounds with totally different structures produce the same odor. Same odor arises because these compounds may interact with receptors to create similar sensory impressions in the sensory centers of the brain. So the role of receptors, i.e., the site of action of the compound, is of critical importance. The compounds react with receptors to produce the olfactory result. Odorant molecules usually contain both a strong hydrophobic and a relatively weak polar region. The latter, usually termed the "osmophore", is associated with a functional group such as carbonyl, hydroxyl, occasionally ether or a limited variety of heteroatomic homologues. However, the presence of a functional group is not necessarily a prerequisite for odor. Even alkanes can have pronounced odors. So Ohloff postulated that substructure elements rather than functional groups should be regarded as osmophores [19]. Odorants present a distinct structure-activity relationship; small structure modifications can influence decisively the odor quality and strength. Here the immediate molecular environment of the osmophoric group appears to play an important role. For example, a simple transposition of the osmophore can lead to a drastic change in odoriferous properties. β-Ionone (**a**) has the characteristic fragrance of violets, whereas β-damascone (**b**) [21] in equal concentration exhibits a completely different and complicated odor profile in which fruity-flowery, exotic-spicy and chrysanthemum-like elements predominate. In some sense, the olfactory character of an organic compound is somehow a function of the spatial arrangement of the molecule, and that is further influenced by its electronic and hydrophobic properties [19].



(**a**)



(**b**)

Computational methods

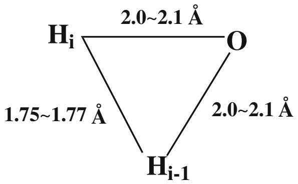
All calculations were performed using the Gaussian 03 program package [22]. We optimized geometries and calculated the harmonic vibrational frequencies for some ambergris odor compounds at the HF/6-31G(d) level of theory, where HF is the restricted Hartree-Fock (RHF)and 6-31G(d) [23] is the used basis set. 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.

Results and discussion

Today there are many known ambergris substitutes with development of organic synthesis. Herein we only started with a series of well studied experimentally compounds possessing ambergris odor to look for an alternative structure-ambergris odor relationship. Good experimental knowledge about the compounds is very important providing information for their most adequate characterization and better predictions. For this purpose such compounds were chosen in this paper: **3**, **5**, and **6** (Fig. 1), **7**–**15** (Fig. 2). Compounds **3**, **5**–**11** were included as representatives of tricyclic ethers. Timberol (**12**) and 4-isopropenyl-1, 3, 3, 5, 5-pentamethylcyclohexanol (**13**) were chosen because the organoleptic properties of their two geometric isomers are known. For Timberol (**12**), Ohloff [24] has demonstrated that it is only the *trans*-isomer which possesses an ambergris-woody odor and that the *cis*-isomer has a much weaker, indefinable floral character (**12a** and **12b** respectively, Fig. 3). For the *trans*- and *cis*-isomers of compound **13** (**13a** and **13b** respectively, Fig. 3), Hoffman and Pauluth [12] confirmed that it is the *cis*- isomer which possesses an ambergris odor. Some Karamal (**14**) isomers were chosen because they provide good examples of active and inactive non-trans-decalin compounds. The structural requirements are further complicated by stereochemical considerations. Karanal (**14**) is a mixture of eight pairs of enantiomers. The diastereoisomeric pairs have been separated by efficient fractional distillation and it has been shown that only four are organoleptically active (three of strong intensity and one of weak). Some of the Karanal representative isomers are shown in Fig. 3 (**14a**–**14c**). Cyclohexyltetrahydrofuran (**15**) was chosen because it provides a good example of active non-decalin compounds. The optimized structures of all compounds are displayed in Fig. 4.

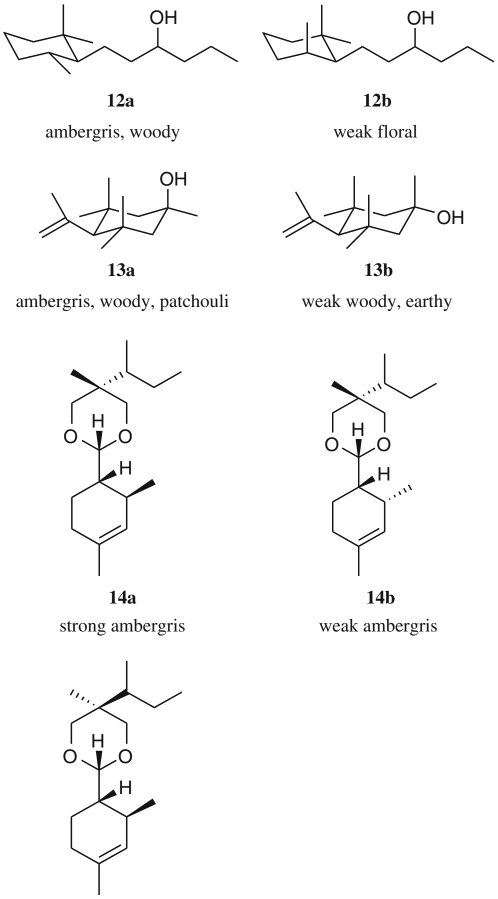
As Vlad [15] suggested, the analysis based on structural and stereochemical features only (bond lengths and angles, distances between specific atomic groups, etc.) is not enough to establish features of origin of ambergris odor. So the electronic structure analysis, such as the atomic contribution to the highest occupied molecular orbital (HOMO) or lowest unoccupied molecular orbital (LUMO), is introduced in this paper to reveal combined electronic, structural and stereochemical features responsible for the ambergris odor.

Geometry optimization and electronic structure analysis revealed that all eight active tricyclic ethers **3**, **5**–**11** and the cyclohexyltetrahydrofuran (**15**) possess such a definite structural fragment: a triangular arrangement of atoms, one being oxygen and the other two hydrogen atoms. To distinguish this "triangle" from the above-mentioned "triangle" of Vlad's, hereafter our "triangle" referred to as "new ambergris triangle". The geometric and electronic characteristics of the "new ambergris triangle" are presented in Table 1. The layout of the "new ambergris triangle" is shown in structure III.



III "new ambergris triangle"

There are also several criteria which apply to these three atoms are worthwhile to be mentioned here. The three atoms must make a major contribution to the HOMO of the molecule or to an occupied orbital lying close to the



12a
ambergris, woody

12b
weak floral

13a
ambergris, woody, patchouli

13b
weak woody, earthy

14a
strong ambergris

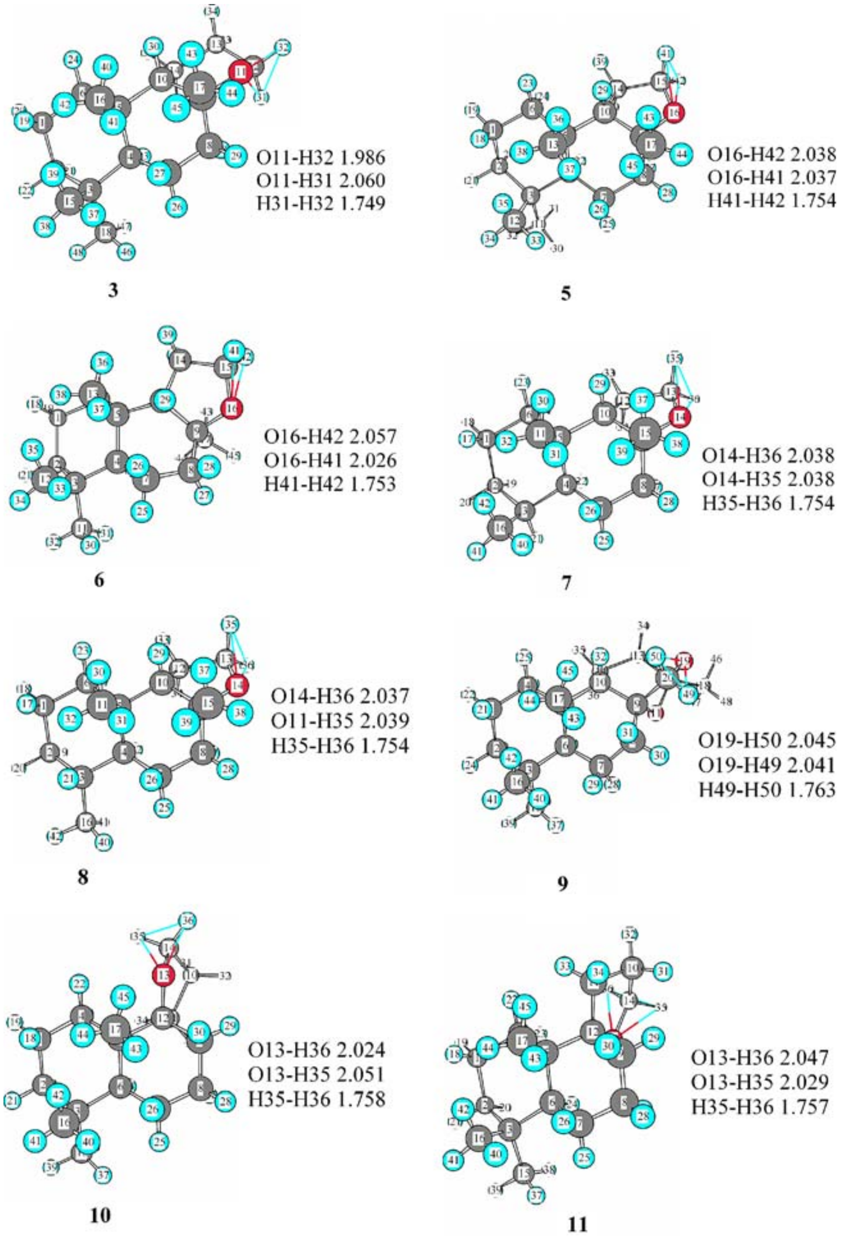
14b
weak ambergris

14c
odorless

Fig. 3 The geometric isomers of compounds 12, 13, and some of the Karanal representative isomers

HOMO; the two hydrogen atoms are bonded to the carbon atom adjacent to oxygen atom; the distances from the two hydrogen atoms to oxygen are close. Furthermore, for the same pair of enantiomers (**5** and **6**, **7** and **8, 10** and **11)**, the closer these two distances are, the stronger the odor of the isomer. For example, for the two pairs of enantiomers of **5** and **6**, **7** and **8,** the distances of O16-H42 (2.038 Å) is closer to that of O16-H41 ((2.037 Å) in **5,** correspondingly, the odor threshold value of **5** (0.3 ppb) is smaller than that of **6 (**34 ppb) [25]. The distance of O14-H36 is equal to that of O14-H35 in **7**, experimental results show that the odor intensity of **7** is virtually stronger than that of **8** [25]; the negative charge of the oxygen atom varies from −0.64 to −0.69; the charges on the two hydrogen atoms are almost identical and varies from 0.13 to 0.17; Mulliken charge density over the triangle should be about $-0.2e/\text{Å}^2$. It should be mentioned that we have attempted to use this rule to explain the odor properties of some monocyclic or bicyclic molecules, including the *trans*- and *cis*-isomers of 1-[2,2,6-trimethylcyclohexanyl]hexan-3-ol (**12a** and **12b** respectively), *trans*- and *cis*-isomers of 4-isopropenyl-1, 3, 3, 5, 5-pentamethylcyclohexanol (**13b** and **13a** respectively), the three active and inactive Karanal isomers (**14a**, **14b**, and **14c** respectively). However, for the monocyclic **12a**, **12b**, **13a** and **13b**, the rule is not applicable unfortunately, because the number of hydrogen atoms bonded to the

Fig. 4 The optimized structures of all investigated compounds

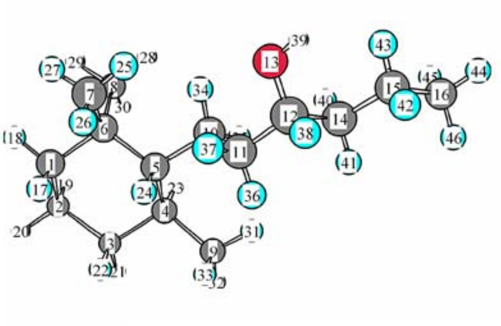


3 **5**

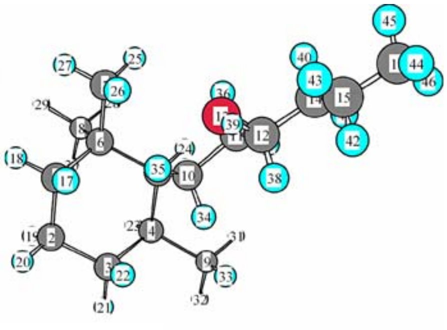
6 **7**

8 **9**

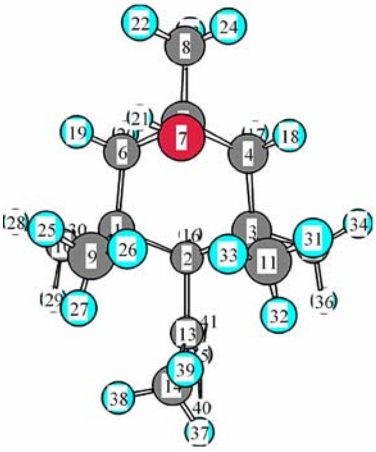
10 **11**



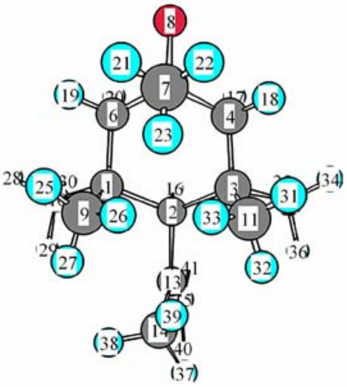
12a



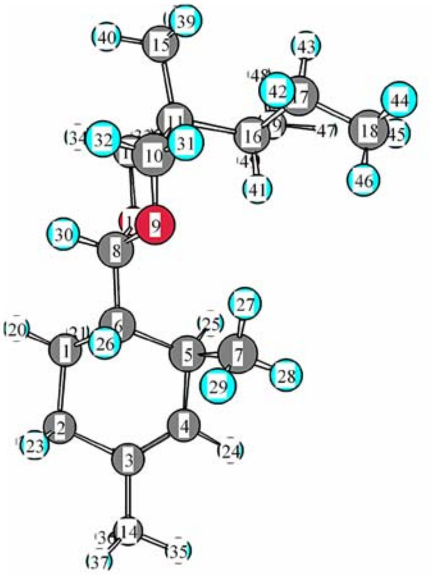
12b



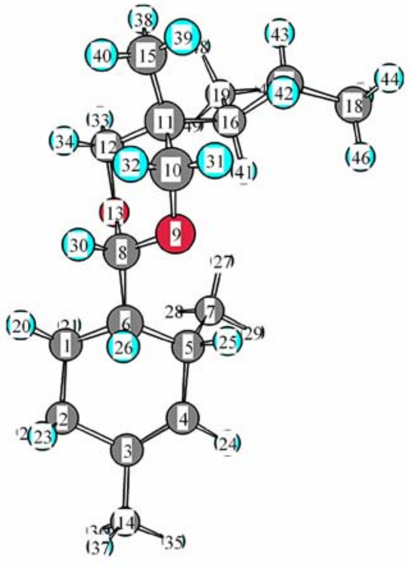
13a



13b



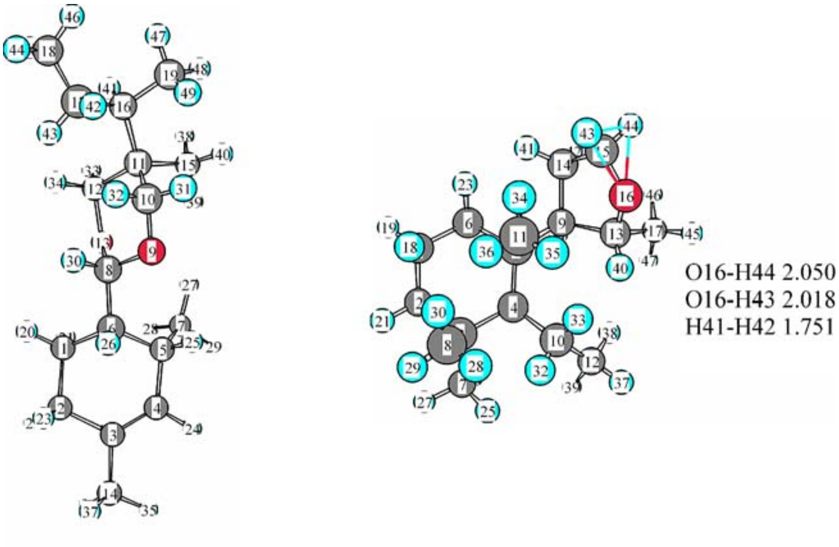
14a



14b

carbon atom adjacent to the oxygen atom is less than 2 (see Fig. 4). For the investigated Karanal isomers, it is not applicable either, because the atomic contribution of one of hydrogen of the triangle to HOMO is not large enough. However, the rule is applicable to cyclohexyltetrahydrofuran (**15**) even if it is a bicyclic molecule. This trend may be attributed to its structure being similar to tricyclic ether (one of its ring may be regard as an opened ring). Therefore, our "new ambergris triangle" rule seems applicable only to the tricyclic ethers.

To further investigate the influence of the FMO on the odor intensity of odorant molecules, we have computed the



14c **15**

Fig. 4 Continued

HOMO-LUMO energy gaps of all the investigated compounds. The corresponding results are listed in Table 2. Compared with the experimental results, we found such a rule: for different isomers of the same compound, the larger the HOMO-LUMO energy gap is, the weaker the odor of the isomer. Since FMO is the molecule's activity region, it seems that the occurrence of such phenomenon is not fortuitous. On the other hand, the total energies of all investigated active and inactive molecules are also listed in Table 2. Table 2 shows that there is no positive connection between odor intensity and isomer's total energy. That is to say, it is not sure that the odor intensity of the lowest energy isomer is the strongest among all different isomers. Examples include isomers **7** and **8**, **10** and **11**. This result is consistent with that of Gorbachov and Rossiter [8].

Summary

In this paper, the structural and stereochemical characteristics, as well as the electronic properties of some typical active and inactive ambergris compounds have been investigated. The following method to predict the presence or absence of ambergris odor in chemical compounds can be proposed: single out in the compound under consideration an oxygen atom and two hydrogen atoms bonded to the carbon atoms adjacent to the oxygen atom; determine the interatomic distances between these atoms and the atomic contributions to HOMO. If all structural and electronic features satisfy the requirements of the "new ambergris triangle", the compound may have the ambergris odor. Otherwise, it would be odorless. On the other hand,

Table 1 Characteristics of the "new ambergris triangle" in compounds 3, 5–11, and 15

Structure	Mulliken Charges on atoms			C_K[a] of 1 s AO's of atoms H_i and H_j		S_{tr}[b], Å^2	σ [c], e/Å^2
	O	H_{i-1}	H_i	H_{i-1}	H_i		
3	−0.67	0.13	0.17	0.173	−0.167	1.59	−0.23
5	−0.68	0.15	0.16	−0.243	0.193	1.61	−0.23
6	−0.68	0.16	0.16	0.194	−0.239	1.62	−0.22
7	−0.68	0.15	0.16	−0.244	0.193	1.61	−0.23
8	−0.68	0.15	0.16	−0.245	0.190	1.61	−0.23
9	−0.68	0.16	0.16	0.135	−0.119	1.62	−0.22
10	−0.69	0.14	0.17	0.232	−0.137	1.62	−0.23
11	−0.68	0.17	0.14	−0.148	0.232	1.62	−0.23
15	−0.64	0.16	0.15	−0.181	0.249	1.61	−0.21

[a] Here C_K is the coefficient of the respective AO in HOMO. [b] Here S_{tr} is the area of the triangle.
[c] Here σ is the mulliken charge density over the triangle.

Table 2 The calculated HOMO and LUMO energies, HOMO-LUMO energy gaps, total energies (E), and odor intensity of the investigated molecules

	HOMO (Hartree)	LUMO (Hartree)	energy gap (kcal/mol)	Odor intensity	E (Hartree)
3	−0.37610	0.21305	369.7	strong	−736.07810
5	−0.38201	0.20925	371.0	0.3*	−697.05173
6	−0.39205	0.20531	374.8	34*	−697.03289
7	−0.38296	0.20876	371.3	12*	−658.02163
8	−0.38205	0.21512	374.7	75*	−658.02806
9	−0.38608	0.20800	372.8	strong	−848.81101
10	−0.37264	0.21367	367.9	relatively strong	−697.05098
11	−0.37426	0.21769	371.5	weak	−697.05447
12a	−0.39586	0.21490	383.3	32*	−660.35426
12b	−0.39839	0.21546	385.2	240*	−660.35326
13a	−0.33705	0.18509	327.6	odor	−620.11804
13b	−0.34245	0.17992	327.8	odorless	−620.11097
14a	−0.32350	0.19851	327.6	strong	−810.93671
14b	−0.32520	0.19985	329.5	weak	−810.93400
14c	−0.32466	0.20087	329.8	odorless	−810.93188
15	−0.38706	0.20573	372.0.	strong	−698.18804

*Odor threshold value (ppb)

for different isomers of the same compound, the larger the HOMO-LUMO gap is, the weaker the odor of the isomer. Our study shows that the lowest energy isomers may not have the strongest odor among all different isomers.

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