Structure–ambergris odour relationship investigation in a mixed series of decalin and non-decalin compounds: the electronic-topological approach

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A series of 201 compounds with decalin- and non-decalin-type skeletons has been investigated by means of the electronic-topological method (ETM) regarding the possession of ambergris odour. A structural fragment of activity (FA2) has been identified, which is a refinement of an activity feature (FA1) obtained as a result of an earlier electronic-topological study of the structure–odour relationship in a series of decalin-type compounds. The FA2 fragment consists of an oxygen atom and five carbon atoms situated in both decalin and cyclohexane parts of the molecules and possesses well-defined three-dimensional (3D) topology and strictly defined electronic characteristics. The applicability of FA2 to compounds with mixed odours is discussed as well.

A large number of articles, including reviews,[1–4] have been devoted to determining and discussing relationships between structure and odour. In a historical perspective, there are multiple works by Ohloff and co-workers[5–7] and Winter[8] devoted to a systematic study of ambergris odour; papers by Jurs and co-workers.[9–11] on structural descriptors for musk odour determination; and research by Buchbauer and co-workers.[12–14] on sandalwood odour prediction. Among these publications can be found, along with theoretical investigations, some works related to the synthesis of new odorants and discussions about olfactory mechanisms, as well. The main goal of this research is to make the purposeful search and design of new substances with a given odour much easier.

The present paper continues some earlier investigations on the structure–odour relationship (SOR) carried out for ambergris odour. Thus, we previously reported on the SOR study of a series of 163 compounds with mainly *trans*-decalin-type skeletons (82 of them possessing ambergris odour, 81 having no ambergris odour).[15] Their conformational and electronic characteristics were calculated and used as input data in the framework of an electronic-topological method (ETM).[16,17] Use of the ETM revealed an activity feature (referred to as the FA1 hereafter). Since some new data on the synthesis of new ambergris odorants and ambergris odour determination have since appeared, we were interested in reviewing the previously obtained results by carrying out the electronic-topological study at a new level using perfected software for the ETM.

Methods

The electronic-topological method (ETM)[18] was proposed in 1985 and since that time has been under permanent improvement, especially its mathematical foundations and software implementation.[16,19] Since details of the ETM can be found in the literature,[16–19] we give here only those properties of the ETM that distinguish it from other methods used to unravel structure–activity relationships (SAR).

Methods developed for predicting the activity of compounds fall into two groups. Indirect, or quantitative SAR (QSAR) approaches rely on establishing functional relationships between the physical chemical properties of the molecules and the activity of interest. The QSAR equations obtained by this are further used for the *quantitative* estimation of the studied activity. A more fundamental approach is to look at the chemical structure of a molecule, that is to search for structural features (molecular substructures and their combinations) common to all active compounds. The features, if successfully found, are used to predict the biological activity (active/inactive or *qualitative* estimation). In order to carry out this type of search, the structure of molecules needs to be described in some way. The compound structure description language (CSDL) used has a significant effect on the predictive ability of the SAR developed.

The ETM is a structure-based method that shares the most promising features of the descriptive centers method[9,20] and topological approach[21] but, in contrast to them, is based mostly on quantum chemical data instead of integral physical chemical characteristics. It uses the so-called electronic-topological matrices of conjunction (ETMC) as the CSDL. An ETMC is an $n \times n$ matrix (n is the number of atoms in the molecule) with its diagonal elements being values of an atomic property such as atomic charge, for example. Its off-diagonal elements are values describing a bond property (if the bond exists); otherwise, they are distances for corresponding pairs of atoms. As the bond property, Wiberg's indices (in electron units, e.u.)[22] are often chosen, because they reflect the bond strength and, together with atomic charges and 3D distances (in Å), give valuable information on the electron density distribution in the 3D space of a molecule.

To begin the ETM study, one must have a representative series of compounds. The measured activity can be either qualitative (*i.e.* active/inactive, in which case there are two classes for comparison) or quantitative (in which case there are more than two classes). Ideally, half of the compounds should be inactive. The main steps of the ETM study are then as follows. (1) For all compounds, calculate spatial and electron parameters for atoms and bonds. (2) For every molecular structure, form an ETMC by taking its elements from the data calculated. (3) Set some desirable level for the activity predic-

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tion and some limiting values ($d1$, $d2$, $d3$) used to find pairs of congruent atoms, bonds and distances. (4) By comparing all ETMCs with an ETMC for the most active compound, select structural fragments S_i, $i \in I$, that are common to all active compounds. (5) Estimate the fragments selected ("activity features") in accordance with a probabilistic criteria (P) and choose those which correspond to the set level of prediction. If the fragments found are not informative enough, change some initial settings (or all of them) and repeat steps 3–5.

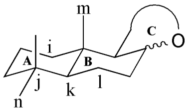
If successfully found for a teaching set and subsequently proven for a validation set, the features S_i can be used to predict the activity of interest (A) for a new series of compounds with the help of the criteria P estimating each structural feature: $S_i \rightarrow_P A$. This expression means that the presence of the feature S_i in a compound implies the activity of the compound with some probability P defined at the final step of the activity features selection. A criteria that is commonly used in structural methods for evaluating the probability for a series under examination is given by $P = (l_1 + 1)/(l_1 + l_2 + 2)$, where l_1 and l_2 are numbers of molecules possessing and not possessing, respectively, a feature of activity in the class of active compounds.

Results and discussion

Analysis of electronic-topological characteristics found previously for ambergris odour

In our previous study,[15] optimized geometry data and electronic characteristics were used in ETMCs formed for all compounds from a series of 163 molecules, in accordance with the main steps of the ETM study. Effective charges on atoms (Q_i) were chosen as diagonal elements (local atomic characteristics); for off-diagonal elements, either bond characteristics (Wiberg's indices, W_{ij}) or optimized distances (R_{ij}, in Å) were used (for chemically bonded and chemically non-bonded pairs of atoms, respectively). In order to have more stable activity features, every active compound was used as a template for comparison with the rest of the ETMCs. As a result of this comparison, an activity feature (*i.e.* molecular fragment that only could be found in active compounds) was revealed (see Fig. 1). The probability P of the feature's presence in active compounds was estimated as 0.95. Hereafter the feature will be referred to as the activity feature FA1.

FA1 consists of two molecular fragments (FA1a, FA1b), which are shown in Fig. 1 as two unjoined submatrices of the ETMC for the representative template compound. The FA1a fragment includes an oxygen atom and carbon atoms from the rings A and B; the oxygen atom must be bonded to a secondary or tertiary carbon atom. FA1b contains two methyl (or methylene) groups that are attached to quaternary carbon atoms and possess similar steric orientation.



O	C_i	C_j	C_k	C_l
$-0.26 \pm d1$	$5.15 \pm d2$	$5.90 \pm d2$	$4.90 \pm d2$	$4.10 \pm d2$
	$0.04 \pm d1$	$3.02 \pm d3$	$2.55 \pm d3$	$3.93 \pm d3$
		$0.05 \pm d1$	$0.97 \pm d3$	$2.60 \pm d3$
			$0.04 \pm d1$	$1.01 \pm d3$
				$0.01 \pm d1$

FA1a

$d1 = 0.03$
$d2 = 0.75$
$d3 = 0.25$

FA1b

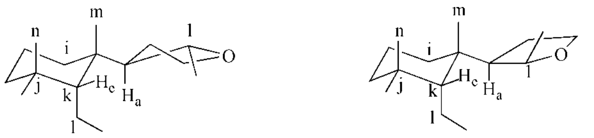
C_m	C_n
$0.01 \pm d1$	$3.45 \pm d3$
	$0.02 \pm d1$

Fig. 1 The activity feature FA1 found for compounds with decalin skeleton.

Let us consider an example of FA1 realization in one representative compound (**I**) of a new class of compounds with a cyclohexyltetrahydrofuran skeleton,[15] which possesses an ambergris odour.[23] In contrast to compounds with decalin skeletons, this active compound has only one cyclohexane ring. This compound has two isomers with either *R* or *S* configurations relative to C_1 in the tetrahydrofuran ring. Realization of the FA1 is shown in Fig. 2. The values given nearby are distances (in Å, here and elsewhere below) between the oxygen and each of the carbon atoms of FA1 in 3D space.

It appeared, however, that in the case of non-decalin systems FA1 did not allow activity to be predicted unambiguously, as, for example, in the case of the stereoisomers (**IIa**, **IIb**) of 4-isopropenyl-1,3,3,4,5,5-pentamethylcyclohexanol.[24] As seen from Fig. 3, the FA1 is realized in both *cis* (**IIa**) and *trans* (**IIb**) configurations of the compound. The stereoisomer **IIa** possesses ambergris odour, while **IIb** does not. Observations such as these have led to further SOR investigations on mixed series containing decalin- and non-decalin-type systems.

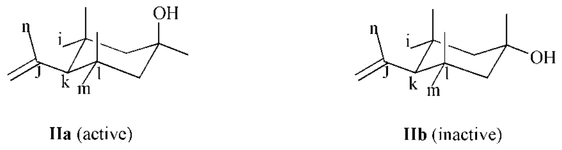
One of the recent papers devoted to monocyclic (non-decalin-type) compounds deserves special attention.[25] There the teaching set included 9 active compounds and 1 inactive compound (*i.e.* 10 in all). The activity feature selection was done by means of a mathematical technique known as pattern recognition. The fragment selected is presented in Fig. 4. Here it is necessary to note that in order to obtain meaningful statistical results by means of a pattern recognition technique, the number of compounds in the teaching set must be representative enough (for example, 40–50 compounds). In addition, the number of active compounds in the teaching set must be comparable with the number of inactive ones (as a rule,



Ia (*R*)
O–i = 4.84
O–j = 6.22
O–k = 4.70
O–l = 4.96
m–n = 3.60

Ib (*S*)
O–i = 4.88
O–j = 6.16
O–k = 4.60
O–l = 4.56
m–n = 3.50

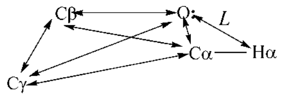
Fig. 2 Feature FA1 realization in **Ia** (*R*) and **Ib** (*S*) isomers of cyclohexyltetrahydrofuran.



IIa (active)
O–i = 4.55
O–j = 6.06
O–k = 4.90
O–l = 3.60
O–m = 4.54
O–n = 5.29
m–n = 3.71

IIb (inactive)
O–i = 4.78
O–j = 5.73
O–k = 4.20
O–l = 3.80
O–m = 4.82
O–n = 6.55
m–n = 3.72

Fig. 3 Feature FA1 realization in isomers of 4-isopropenyl-1,3,3,4,5,5-pentamethyl cyclohexanol.



O	C_α	C_β	C_γ
−0.27 ± 0.08	2.4 ± 1.0	4.2 ± 0.4	5.2 ± 0.4
	.06 ± 0.1	4.9 ± 0.6	5.1 ± 0.7
		.00 ± 0.02	3.2 ± 0.7
$L = 2.8 \pm 0.5$			0.01 ± 0.02

Fig. 4 The "active ambergris fragment" (AAF) found by Gorbachov and Rossiter.[25]

approximately half of the compounds should be active). Otherwise, this method can cause a high percentage of error when being applied to a validation set.

From Fig. 4 it follows that the "active ambergris fragment" (AAF) contains an oxygen atom and three carbon atoms (C_α, C_β, C_γ) with certain atomic charges (in e.u.) that are separated by certain "key distances". The C_α atom cannot be a quaternary carbon because it must bear at least one hydrogen atom, hereafter referred to as H_α. L is the distance between H_α and one of the unshared electron pairs of the oxygen atom.

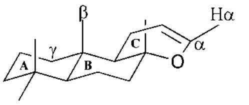
The AAF classifies compounds from the Karanal series and some other compounds containing a cyclohexane ring. Unlike Gorbachov and Rossiter, we found that the AAF is also realized in most of the inactive compounds with decalin-type skeletons. We believe that these differences may be attributed to the algorithm used by them. Some examples showing the presence of the AAF in inactive decalin compounds are provided below (**III–V**). Original notation[25] is retained for compounds used in the examples and all other figures related to the AAF discussion. Thus, in Fig. 5 the AAF presence is demonstrated for one active (**IIIa**) and one inactive (**IIIb**) compound with similar structure. In Fig. 6 the AAF realization is demonstrated for four compounds (**IVa** is active, **IVb–d** are inactive). As seen from Fig. 6, the removal of one or two methyl groups from the quaternary carbon atom causes loss in activity (see also Ohloff *et al.*[6]). At the same time, all changes in the geometrical and electronic characteristics of the AAF are within the allowable limits. In conclusion, an example of the AAF realization in two inactive compounds with different skeletons, **Va** and **Vb**, is shown in Fig. 7.

From the given examples one can conclude that carbon atoms in the AAF are determined ambiguously (note that in the examples all characteristics of the AAF,[25] *i.e.* charges, distances, *etc.*, are obeyed). This fact causes the AAF to be realized in most inactive compounds. In pattern recognition theory such features are known as "non-dividing", because they allow no division into classes of active and inactive compounds for the molecules under study. Our electronic-topological study of the compounds with decalin skeletons (163 compounds) has shown that 86% of inactive compounds are classified as active by means of the AAF.

The electronic-topological study of a mixed series of decalin- and non-decalin type systems

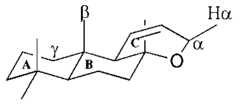
Recently, the number of compounds with non-decalin-type structures known to possess an ambergris odour has increased (see Gorbachov and Rossiter[25] and references cited therein). Thus, it was of interest to study in detail those compounds that contain a cyclohexane ring but which differ in their substituents. For a mixed series of molecules with both decalin- and non-decalin-type structures (201 compounds) the electronic-topological study has been carried out again. All conformational and quantum-chemical data have been obtained by means of the MM2P[26] method of molecular mechanics and the semi-empirical quantum-chemical methods CNDO[27] AM1 and PM3.[28] Activity feature selection has been carried out by means of the perfected ETM software.[16,19]

The activity feature found is given in Fig. 8. In the subsequent discussion it will be referred to as the activity feature FA2. As seen from Fig. 8, the main characteristics of the FA1 feature do not change. But the fact that oxygen is situated at definite distances from atoms C_m and C_n is found to be very important for the successful prediction of the odour activity.



IIIa (active)

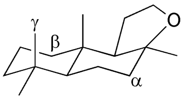
O–α = 1.37
O–β = 4.57
O–γ = 4.96
α–β = 5.06
α–γ = 5.17
β–γ = 2.53



IIIb (inactive)

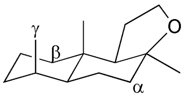
O–α = 1.42
O–β = 4.53
O–γ = 4.92
α–β = 4.89
α–γ = 5.30
β–γ = 2.51

Fig. 5 Influence of the position of the double bond in cycle C on the activity of compounds **IIIa** and **IIIb**.



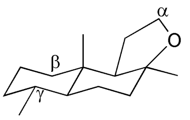
IVa (active)

O–α = 2.40
O–β = 4.58
O–γ = 5.60
α–β = 4.40
α–γ = 4.60
β–γ = 3.90
$L = 2.60$



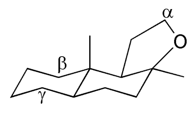
IVb (inactive)

O–α = 2.40
O–β = 4.56
O–γ = 5.60
α–β = 4.42
α–γ = 4.61
β–γ = 2.54
$L = 2.49$



IVc (inactive)

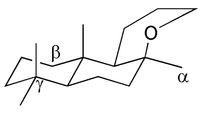
O–α = 1.42
O–β = 4.56
O–γ = 5.16
α–β = 4.40
α–γ = 5.75
β–γ = 2.97
$L = 2.40$



IVd (inactive)

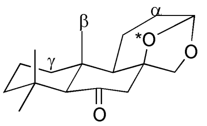
O–α = 1.42
O–β = 4.57
O–γ = 5.12
α–β = 4.42
α–γ = 5.70
β–γ = 2.95
$L = 2.41$

Fig. 6 Influence of methyl groups on the presence of ambergris odour. (compounds **IVa–d**)



Va (inactive)

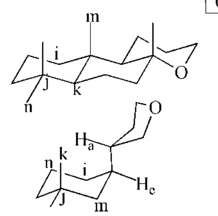
O–α = 2.45
O–β = 4.63
O–γ = 5.39
α–β = 5.01
α–γ = 5.69
β–γ = 3.01
$L = 2.83$



Vb (inactive)

O–α = 2.40
O–β = 4.01
O–γ = 4.92
α–β = 4.50
α–γ = 4.48
β–γ = 2.50
$L = 2.47$

Fig. 7 AAF realization in compounds **Va,b**.



C_i	C_j	C_k	O	C_m	C_n
$\frac{0.01}{0.07}$	$\frac{2.27}{3.27}$	$\frac{2.30}{2.95}$	$\frac{4.40}{5.90}$		
	$\frac{0.02}{0.08}$	$\frac{0.90}{1.10}$	$\frac{5.15}{6.65}$		
		$\frac{0.01}{0.07}$	$\frac{4.15}{5.65}$		
			$\frac{-0.23}{-0.29}$	$\frac{3.30}{4.60}$	$\frac{4.80}{5.75}$
				$\frac{-0.02}{0.04}$	$\frac{3.00}{3.90}$
					$\frac{-0.01}{0.05}$

Fig. 8 The activity feature FA2 resulting from the study of the mixed series of compounds. The matrix contains lower (numerator) and upper (denominator) limits for the corresponding values of the feature's parameters that allow the molecule to be active.

In other words, the two separate structural fragments found before[15] as the activity feature FA1 appear to be strongly connected in the FA2. The other distinction of the FA2 is that it no longer contains the C_1 atom (see Fig. 1). This is due to the fact that many compounds in the mixed series are monocyclic.

Now the absence of the ambergris odour in the case of *trans*-isomer **IIb** becomes quite clear from the FA2 characteristics: the distances between oxygen and each of the atoms C_m, C_n do not correspond to the key distances of the FA2. For *cis*-isomer **IIa**, however, the distances are respected (see Fig. 3).

Let us look at one more interesting series of compounds[29,30] (their SORs were discussed previously[25]). As an example, we want to show the FA2 realization in two active compounds (**VIa**, **VIb**) and one inactive compound (**VIc**) from this series (see Fig. 9). In the given series, active compounds differ from inactive ones with respect to the position of their *sec*-butyl group. Steric alignment of the hydrogen H_1 by the atom C_1 (as well as of the CH_3 group by the atom C_2) does not considerably influence the odour's presence or absence.

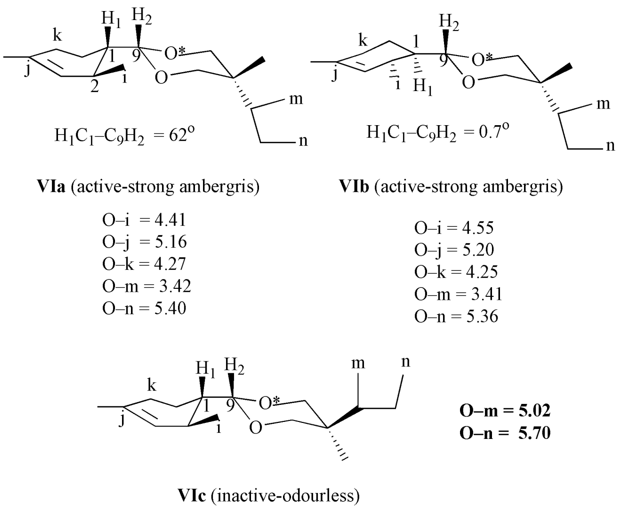


Fig. 9 The feature FA2 applied to the Karanal series.

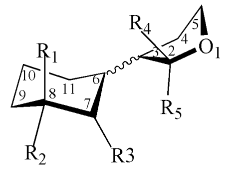
With the appropriate activity feature FA2 in hand, we were interested in shifting emphasis from the theoretical study to the synthesis of new derivatives[31] of cyclohexyltetrahydrofuran that could be checked against the ambergris odour with the help of rules derived from the properties of the FA2. The derivatives are presented in Table 1 with their common skeleton. Organoleptic testing of the synthesized compounds has been done by experts[32] and their odour characteristics are given in Table 1 as well. The compounds have been obtained as mixtures of diastereomers in racemic forms. Their separation by means of chromatographic or other methods did not seem possible. Moreover, the compounds could also exist as a mixture of conformers obtained as a result of reversible conversion of cyclohexane and tetrahydrofuran rings.

The result of the mixed series investigation showed that only three of the compounds, namely **3**, **6** and **9**, contained the FA2. Organoleptic evaluation has shown that just these three compounds have in their odours a dominant ambergris note. In this way, the results of theoretical and experimental studies are in agreement.

Because straightforward experimental separation of the racemates is impossible, let us consider a theoretical way of determining the odour of each stereoisomer through the FA2 realization in its structure. In Table 2, structures of all possible isomers are given with regard to the type of cyclohexane and tetrahydrofuran ring attachment. For compound **6**, there exists an opportunity of forming four pairs of enantiomers due to either an *R* or *S* configuration of the methyl group in the tetrahydrofuran ring. We discuss here the FA2 realization in each of the enantiomers from Table 2 (see Fig. 10). The FA2 is realized in compounds **3c** and **3d** (*ea*, *ae* attachments). For two other conformers (**3a** and **3b**) some of the geometric characteristics of FA2 (indicated in bold type) go out of the allowable limits. Therefore, they were classified as structures with no ambergris odour.

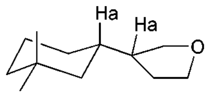
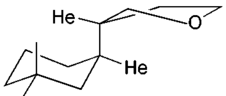
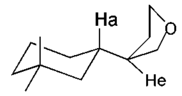
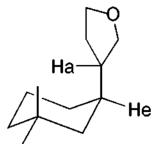
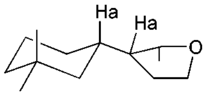
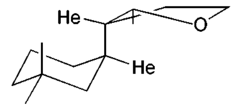
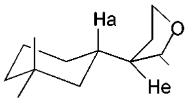
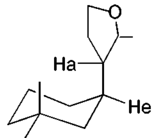
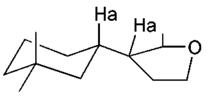
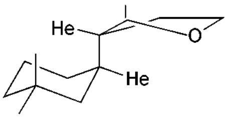
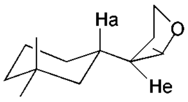
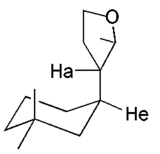
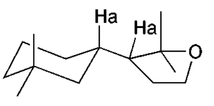
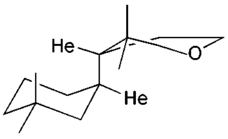
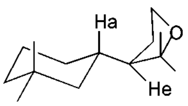
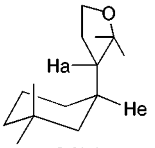
As for compounds **6a**–**d**, the FA2 is found in the molecules **6c** (*ea*) and **6d** (*ae*). With respect to the other four stereoiso-

Table 1 Synthesized compounds and characterization of their odour



Compound	R_1	R_2	R_3	R_4	R_5	Number of isomers	Odour characterization
1	H	H	H	H	H	4	Intense smell of greens, chemical tonality
2	H	H	CH_3	H	H	8	Flower (iris) with the fruit note, turpentine-like tonality
3	CH_3	CH_3	H	H	H	4	Ambergris odour with woody and flower notes, musk tonality
4	H	H	H	CH_3	H	8	Intense woody, turpentine-like odour
5	H	H	CH_3	CH_3	H	16	Intense woody, with ambergris and turpentine-like tonalities
6	CH_3	CH_3	H	CH_3	H	8	Ambergris odour with weak greasy tonality and woody note
7	H	H	H	CH_3	CH_3	4	Intense woody, with ambergris note, turpentine-like tonality
8	H	H	CH_3	CH_3	CH_3	8	Woody turpentine-like with ambergris tonality
9	CH_3	CH_3	H	CH_3	CH_3	4	Intense ambergris odour with animal note and balsamic tonality

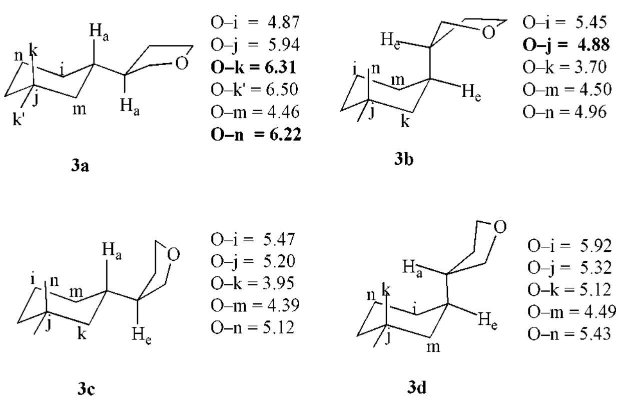
Table 2 Stereoisomers of compounds **3**, **6** and **9** and indication of the presence (+) or absence (−) of the FA2

ee	*aa*	*ea*	*ae*
 3a(−)	 3b(−)	 3c(+)	 3d(+)
 6a(−)	 6b(−)	 6c(+)	 6d(+)
 6e(−)	 6f(−)	 6g(+)	 6h(+)
 9a(−)	 9b(+)	 9c(+)	 9d(+)

[a] Here *e* is the equatorial orientation of H atoms and *a* is the axial one (indirect characterization of the type of cycles connection).

mers (**6e–h**), the FA2 is only found in compounds **6g** and **6h**. In the same way, the FA2 is present in all stereoisomers of compound **9** except **9a**. The FA2 realization in stereoisomers of compounds **3**, **6**, **9** is given in Table 2.

It is worth drawing attention to the fact that in one of the conformers (**3a**, *ee*) the structural fragment responsible for the musk odour[33] is found. Organoleptic evaluation also revealed musk tonality in its odour. As shown in Fig. 10, the "musk fragment" in this compound is formed by two methyl groups (k and k′) attached to the tertiary carbon atom (C_j) and situated *symmetrically* at a definite distance from the oxygen atom. At the same time, compounds **6** and **9** include this musk fragment but have no musk tonality in their odour because of the bulky substituents positioned *ortho* to the oxygen atom (see Rule 2[33]). On the other hand, the growing number of methyl groups in the tetrahydrofuran ring favours better realization of the ambergris feature FA2 in the same compounds (**3**, **6** and **9**). However, simultaneous coexistence of the musk fragment and FA2 in a molecule and correlation of the corresponding notes in the molecule's odour is a very complex question and the subject for further theoretical and experimental studies.

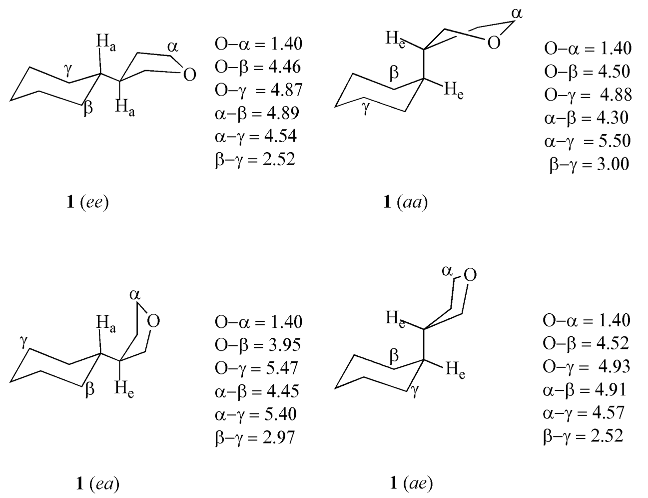


3a **3b** **3c** **3d**

Fig. 10 FA2 realization in compounds **3a–d**.

The highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO), also called frontier orbitals, may well play an important role in the donor–acceptor interaction of a substance with the corresponding receptors. Analysis of HOMOs for the compounds possessing ambergris odour has shown that atoms with the highest values of the atomic orbital coefficients are mainly those atoms that enter into the FA2. This is clearly seen from the molecular orbital (MO) wavefunction given below. It suggests again the important role played by these atoms in the substrate–receptor interaction. For convenience, we have used $|\Psi|^2$, which gives the charge distribution on the atoms contributing to the HOMO (their numbers are taken from the structure in Table 1).

$$|\Psi|^2_{\mathrm{HOMO}} = 0.03\mathrm{O}_1 + 0.07\mathrm{C}_2 + 0.11\mathrm{C}_6 + 0.08\mathrm{C}_7 + 0.07\mathrm{C}_8 + 0.09\mathrm{C}_{11}$$



1 (*ee*) **1** (*aa*) **1** (*ea*) **1** (*ae*)

Fig. 11 AAF realization in four isomers of compound **1** (see Table 1).

Let us have a glance at the AAF (Gorbachov and Rossiter[25]) realization in the class of synthesized compounds given in Table 1. Since the total number of isomers is 64, we take into account only those that differ in the type of bonding between the cyclohexane and tetrahydrofuran rings. When varying the R_1–R_5 substituents attached to these rings, we observe some minor changes in the parameters of the AAF. But, although the changes are within the allowable limits, among the corresponding compounds there are inactive as well as active ones (four isomers of compound **1** are presented in Fig. 11; all are inactive, but the distances between atoms entering the fragment satisfy the AAF's requirements). Thus, it does not seem possible to determine unambiguously the presence (or absence) of the ambergris odour in compounds **1**–**9** (Table 1) with the help of the AAF.

Conclusions

The previously found[15] activity fragment, FA1, has been refined by investigating a mixed series of compounds that includes both decalin and non-decalin systems. The modified activity fragment, FA2, correctly assigns the activity of all the compounds we have studied. The essential difference between FA1 and FA2 is that an oxygen atom appears in the previously found "methyl" fragment of the FA1. In the FA2, two separate fragments of the FA1 appeared to be unified with this oxygen atom. Thus, for the FA2 as well as for the FA1, distances between this oxygen atom and each of the C_i, C_j and C_k atoms play an important role. In addition, the C_j atom must be quaternary. In contrast to the FA1, the methyl fragment in the FA2 can be formed not only by CH_3 groups but also by methylene groups of a cyclohexane ring.

From this study one can conclude that interaction between a molecule possessing an ambergris odour and the olfactory receptors may take place through the hydrophobic and donor–acceptor parts of the molecule. From the FA2 properties it follows that a definite spatial relation must exist between these two parts. As the analysis of frontier MOs shows, the orbital charge control is of extreme importance here. According to the nature of the atoms entering the FA2 feature, the tertiary carbon atom C_j and the atoms C_m, C_n of the "methyl" fragment must fulfill hydrophobic functions in the molecules. The oxygen atom can play the role of the hydrogen bond acceptor. A more detailed study of molecular protein structures of the odour receptors, along with docking of active molecules into them, may in the future clarify the mechanism of their bonding and make the understanding of the phenomena more fundamental.

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