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A New Electronic–Topological Investigation of the Relationship between Chemical Structure and Ambergris Odour

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Abstract

An electronic–topological approach has been used to define an active ambergris fragment (AAF) which correctly describes the presence (or absence) of the ambergris odour of all 181 compounds investigated. The AAF consists of one oxygen atom and three carbon atoms (α, β, γ) which are separated by certain key distances and which possess certain atomic charges. The C_α atom must bear at least one hydrogen atom (H_α) which is located at a certain distance from one of the unshared electronic pairs of the oxygen atom.

Introduction

Since ancient times, ambergris has been one of the most highly valued perfumery materials. It is secreted in the stomach or intestinal tract of the sperm whale and released into the sea in the form of a grey to black stone-like mass. When exposed to sunlight, air and sea water, the material gradually fades to a light grey or creamy yellow colour and, at the same time, the main component, the odourless triterpene alcohol ambrein (**1**, Figure 1), is oxidatively degraded. Some of the products resulting from this chemical process are responsible for the organoleptic properties of ambergris. Since these (**2–3**) and the early synthetic ambergris odorants all contain a *trans*-decalin system, its presence was originally believed to be one of the prerequisites for an ambergris odour and most of the studies into the relationship between chemical structure and ambergris odour have been based solely on this group of compounds (Ohloff, 1971; Vlad *et al.*, 1985a; Winter, 1990; Dimoglo *et al.*, 1995).

However, a few *cis*-decalins smell of ambergris (e.g. compound **4**, Figure 2) (Ohloff *et al.*, 1990), and the number of ambergris odorants which do not even contain a decalin system has rapidly expanded over the past 15 years. Examples include Timberol (**5**) (Klein and Rojahn, 1979; Brunke *et al.*, 1980), cyclohexyltetrahydrofuran (**6**) (Vlad *et al.*, 1985b), 4-isopropenyl-1,3,3,5,5-pentamethylcyclohexanol (**7**) (Hoffman and Pauluth, 1985), Karanal (**8**) (Newman *et al.*, 1988), Ambercore (**9**) (Koshino *et al.*, 1991) and a mixture of 2-(2-bornyloxy)-ethyl-1-ethanols (**10**) (Boden *et al.*, 1994) (Figure 2). Thus the aforementioned structure–odour relationships for ambergris are clearly incomplete.

Dimoglo *et al.* (1995) have attempted to use the rules which they derived from decalin-type systems to explain the odour properties of some monocyclic ambergris molecules, including 4-isopropenyl-1,3,3,5,5-pentamethylcyclohexanol (**7**) and 3-(2-ethyl-1,3,3-trimethylcyclohexyl)-2-methyl tetrahydrofuran (**11**, Figure 3b). In the decalin-type compounds they found that many of the active materials shared two common molecular fragments (Figure 3a). Fragment I

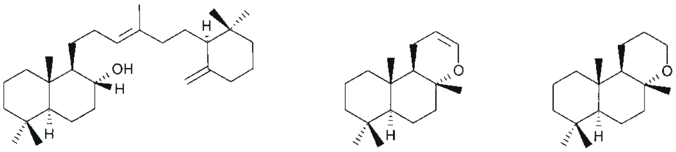


Figure 1 Two ambergris odorants and their natural precursor.

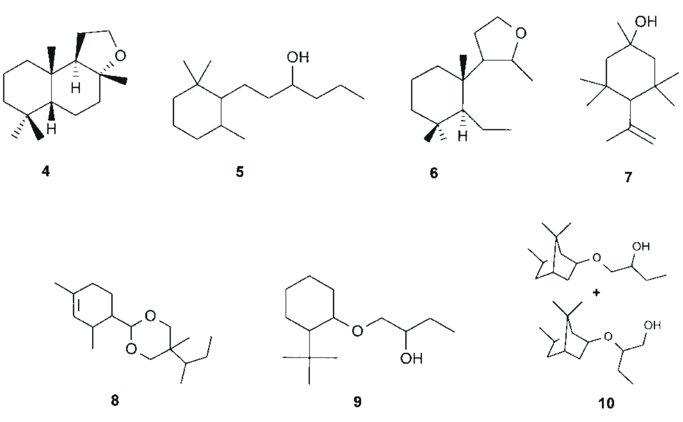


Figure 2 Examples of non-*trans*-decalin ambergris odorants.

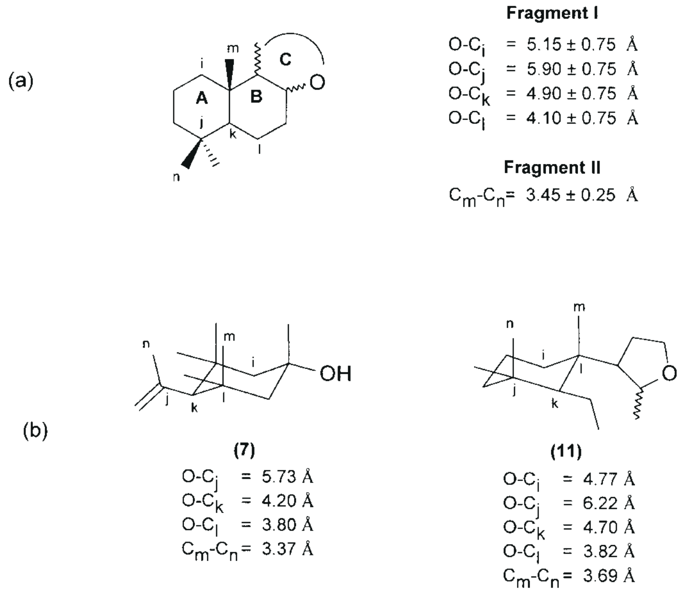


Figure 3 **(a)** The atoms and the distances between them that form Dimoglo's fragments I and II. **(b)** Application of fragments I and II to two non-decalin compounds.

includes an oxygen atom and four carbon atoms from the rings A and B. The distances between these carbon atoms (C_i, C_j, C_k and C_l) and the oxygen atom are ~5.15, 5.90, 4.90 and 4.10 Å respectively. Fragment II contains two methyl groups (C_m and C_n) which have the same stereochemical orientation, are attached to quaternary carbon atoms and are separated by a distance of ~3.45 Å. The effective atomic charges of the oxygen atom and carbon atoms i–n are also important, but for the sake of simplicity are not discussed here. Dimoglo's application of these rules to the monocyclic compounds **7** and **11** is shown in Figure 3b. For some reason Dimoglo has only considered the *trans*-isomer of 4-isopropenyl-1,3,3,5,5-pentamethylcyclohexanol (**7**) despite the findings of Hoffman and Pauluth (1985) that it is, in fact, the *cis*-isomer which possesses an ambergris note. Our own interatomic measurements for *trans*-7 show that the O–C_i distance is only 2.42 Å and thus much too short to meet the fragment I criterion of 4.40–5.90 Å. Our measurements for O–C_j, O–C_k, O–C_l and C_m–C_n are in close agreement with those of Dimoglo *et al.* (i.e. 5.74, 4.20, 3.81 and 3.21 Å respectively). [Note: interatomic measurements were performed using the Cerius2 version 3 software from Molecular Simulations Incorporated. Geometries were optimized using molecular mechanics, forcefield cff95_950_1.01 (Dinur and Hagler, 1991).]

In one of the most recent investigations into the relationships between structure and ambergris odour, Bajgrowicz and Broger included six active non-decalin compounds in their training set of 23 compounds to generate possible ambergris osmophores (Bajgrowicz and Broger, 1995). These osmophores were then tested using a further 121 compounds (45 active, 76 inactive). From six possible osmophores, Bajgrowicz and Broger chose the one which they thought was most plausible from a chemist's point of view. It consisted of a hydrogen-bond acceptor, four hydrophobic regions and six excluded volumes [for a recent review of this work and of other structure–odour relationship studies of ambergris odorants, see Rossiter (1996)].

However, unlike the decalin compounds, where, mainly as a result of the extensive studies by Ohloff and co-workers, there is a wealth of odour data for compounds of defined absolute configuration, the odour data for the non-decalin compounds is rather fuzzy and often refers to isomeric mixtures. For example, the individual odour characteristics of the two positional isomers of 2-(2-bornyloxy)-ethyl-1-ethanol (**10**) have not been reported. The influence of chirality also needs further investigation. Thus it is clear that in order to increase our understanding of the structural requirements for an ambergris odour, more detailed organoleptic data is required.

In the Karanal series, the synthesis and organoleptic evaluation of a large number of analogues enabled the following general requirements for a material in this family to have an ambergris odour to be defined (Sell, 1990). The 5 position of the dioxane ring should be substituted by a methyl group and a more bulky group (e.g. *sec*-butyl, *n*-propyl, *iso*-propyl, *tert*-butyl). The cyclohexane ring should preferably have a double bond in the 3,4 position, although this is not essential and should carry 1–3 methyl groups, preferably 2. However, the location of these seems to be more important than the number.

The structural requirements are further complicated by stereochemical considerations. Karanal (**8**) 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). These findings agree with our gas chromatography olfactometry (GCO) evaluation of the isomeric mixture. GCO is a technique which, provided that the gas chromatography conditions adequately separate the components of a mixture, enables each component to be smelt in an olfactorily pure state at the exit port of a gas chromatography columnWe have been unable to resolve the individual enantiomers of each pair by any standard techniques, including chiral GCO. Chiral synthesis of all eight enantiomers of the four active diastereoisomeric pairs would be laborious and complicated by the fact that the chiral centre at position 2 of the dioxane ring is formed during acetalization and that the proton at C1 of the cyclohexene ring would be racemized during acetalization. Besides, the electronic–topological approach, which we have used to investigate the relationship between structure and ambergis odour, is unable to distinguish between the enantiomers of a racemic pair.

One of the inactive Karanal pairs crystallized on standing, thus enabling us to obtain an X-ray crystal structure.

This, in conjunction with NMR studies, has enabled us to define the stereochemistry of the active and inactive pairs. These data have been used, along with other non-*trans*-decalin compounds and all of the compounds used in the investigations of Vlad *et al.* (1985) and Dimoglo *et al.* (1995), to develop a structure–odour relationship which correctly describes the presence (or absence) of the ambergris odour of all 181 compounds investigated.

Materials and methods

The electronic–topological approach allows the investigation of both the electronic structure and spatial topology of a set of structurally diverse molecules. A detailed account of this approach may be found in the literature (Bersuker *et al*, 1987). In summary, the following sequence of computational calculations are performed:

- Conformational analysis using the MM2 method (Allinger and Burkert, 1982).
- Quantum-chemical calculation of electronic properties using the CNDO/2 method (Segal, 1977).
- Formation of electronic–topological matrices of contiguity (ETMCs). Each compound is represented by an n^2 quadratic matrix, n being the number of atoms. Since this square matrix is symmetrical with respect to its diagonal elements, only the upper half is usually shown. In this study, the diagonal elements are the effective atomic charges and the non-diagonal ones are the optimized interatomic distances. Unlike Dimoglo *et al.* (1995), for the tri- and polycyclic *trans*-decalin compounds, we took into account not only the distances between the oxygen atom of ring C and the carbon atoms of rings A and B (Figure 3a), but also the distances between the carbon atoms of ring C and those of rings A and B.
- Computerized comparison of the ETMCs and activity feature selection using pattern recognition theory (Rosenblit and Golender, 1983) of the atomic charges and interatomic distances in N-dimensional space. The number N is equal to the total number of the atomic charges and interatomic distances in the largest ETMC.

Results

The electronic–topological investigation involved two stages. For the first step, a small restricted set of compounds was chosen: 4-isopropenyl-1,3,3,5,5-pentamethylcyclohexanol (**7**), the active Karanal stereoisomers, the four active molecules (**12–15**, Figure 4) and the inactive one (**16**, Figure 4). Compound **7** was chosen because the organoleptic properties of the two geometric isomers (Hoffman and Pauluth, 1985) are known and because, as a consequence of its symmetry and size, there are only a small number of interatomic distances. Compound **11** (Figure 3b) was chosen because it has the shortest average distance between its oxygen atom and carbon atoms. The Karanal isomers were chosen because of our particular interest in this series of compounds, they provide good examples of active and inactive non-*trans*-decalin compounds and they have never been studied before in an ambergris odour–structure relationship. Compounds **12–16** were included as representatives of the *trans*-decalin family.

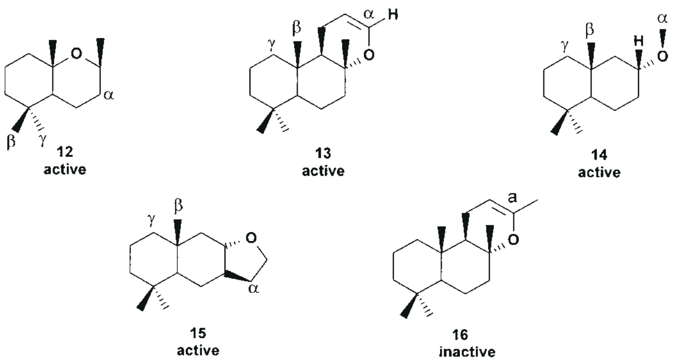


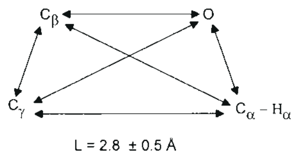
Figure 4 Examples of the *trans*-decalin compounds used in step 1 of the electronic–topological approach.

A computerized comparison of the ETMCs of these 10 compounds revealed that all nine active materials contained the following structural fragment, hereafter referred to as the active ambergris fragment (AAF). The AAF contains one oxygen atom and three carbon atoms (α, β, γ) which are separated by certain key distances and which possess certain atomic charges. The C_α atom cannot be a quaternary carbon since it must bear at least one hydrogen atom (hereafter referred to as H_α). This is nicely illustrated by the comparison of the active and inactive compounds, **13** and **16** respectively (note: for inactive structures the letters α, β and γ are replaced by a, b and c respectively). The upper limits of the distances of the AAF are provided by the active stereoisomers of Karanal and compound **15**.

The study was extended to include, in addition to the 10 compounds studied in step 1, the four inactive Karanal diastereoisomers and all of the compounds used by Vlad *et al.* (1985a) and Dimoglo *et al.* (1995). The chemical structures and associated odour data are listed in these references. The extended data set of 181 compounds allowed the distances and charge criteria for the AAF to be defined more precisely (Figure 5). The distance between the H_α atom and one of the unshared electronic pairs of the AAF's oxygen atom (L), and the steric accessibility of H_α and of the oxygen atom's active electronic pair (AEP) were also found to be important.

Discussion

The AAF correctly describes the presence (or absence) of the ambergris odour for all of the 181 compounds investigated. Its use is best illustrated with a few examples. In these examples the numerical values adjacent to the α, β and γ carbon atoms are the distances between these carbon



O	Cα	Cβ	Cγ	
-0.27 ± 0.08	2.4 ± 1.0	4.2 ± 0.4	5.2 ± 0.4	O
	0.06 ± 0.1	4.9 ± 0.6	5.1 ± 0.7	Cα
		0.00 ± 0.02	3.2 ± 0.7	Cβ
			0.01 ± 0.02	Cγ

Key
diagonal elements are effective atomic charges (e.u.) non-diagonal elements are interatomic distances (Å) L = distance between Hα and the active pair of electrons on the oxygen atom

Figure 5 The active ambergris fragment (AAF) contains one oxygen atom and three carbon atoms (α, β and γ) which are separated by certain key distances (non-diagonal elements in Å) and which possess certain atomic charges (diagonal elements in Hartree's atomic units). L is the distance between the Hα atom and one of the unshared electronic pairs of the AAF's oxygen atom.

atoms and the AAF's oxygen atom. The latter, in the case of polyoxygenated compounds, is marked by an asterisk. The distances between the carbon atoms are listed below each structure and are labelled $L_{\alpha\beta}$, $L_{\alpha\gamma}$ and $L_{\beta\gamma}$ for active compounds, and L_{ab}, L_{ac} and L_{bc} for inactive compounds, where carbon atoms a, b and c are those which most closely fit the requirements for the active carbon atoms α, β and γ respectively. The distance (L) for active molecules is also provided where appropriate.

Let us first consider the *trans*- and *cis*-isomers of 1-[2,2,6-trimethylcyclohexanyl]hexan-3-ol (**5a** and **5b** respectively, Figure 6). Ohloff (1984, 1985) has demonstrated that it is only the *trans*-isomer which possesses an ambergris–woody odour and that the *cis*-isomer has a much weaker, undefinable floral character. NMR evidence suggests that the conformational arrangement of the *cis*-isomer, at least at room temperature and in solution, is such that the hexan-3-ol side chain is in the axial position and the methyl group at C6 is in the equatorial position (Ohloff *et al.*, 1985). In this conformation (**5b-I**), the distance between the oxygen and C_b atom is too long to satisfy the distance criterion of the AAF (4.8Å as opposed to 3.8–4.6Å). Molecular modelling has shown that the reverse *cis*-conformational arrangement (**5b-II**) is also energetically favourable (23.1 kcal/mol compared with 23.5 kcal/mol for **5b-I**), but again the AAF distance criteria are not met, with the distances between the oxygen atom and the carbon atoms b and c being too long. However, in the *trans*-isomer (**5a**) the absence of steric hindrance between the axial methyl group at C6 and the hydrogen atoms of the first carbon atom of the oxygen-containing side chain allows this chain to rotate such that the distances between the oxygen atom and carbon atoms b and c become shorter (4.6 and 5.1Å respectively) and the AAF distance criteria are satisfied.

For the *trans*-isomer of 4-isopropenyl-1,3,3,5,5-pentamethylcyclohexanol (**7b**, Figure 6) one finds that the distance between carbon atoms a and b is too short to meet the distance requirements of the AAF (3.4 Å as opposed to 4.3–5.5 Å). This material does not have any ambergris character but is weak, woody and earthy. On the other hand, the *cis*-isomer with the axial hydroxyl group contains the AAF and possesses, according to Hoffman and Pauluth (1985), an ambergris, woody, patchouli odour.

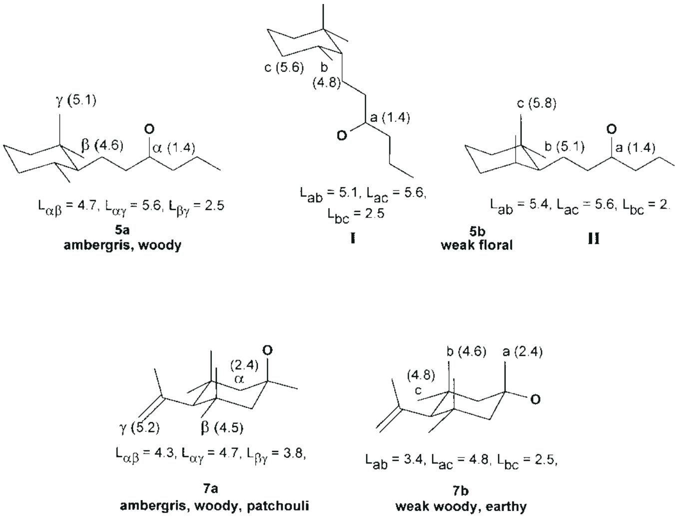


Figure 6 Comparison of *cis*- and *trans*-4-isopropenyl-1,3,3,5,5-pentamethylcyclohexanol. Numerical values adjacent to the carbon atoms are the distances between these carbon atoms and the oxygen atom of the active ambergris fragment (AAF) in angstroms. L_{ij} is the distance between carbon atoms i and j. For the inactive compounds, carbon atoms a, b and c are those which most closely fit the requirements for the active carbon atoms α, β and γ respectively. The distance L_{ab} in the *trans*-isomer (**7b**) is too short to fulfil the AAF criterion of 4.3–5.5Å.

Some more examples of structurally related active and inactive compounds which illustrate the importance of the AAF's distances are provided in Figure 7. The distances which do not meet the AAF criteria are underlined. For example, in compound **24** the distance between atoms C_a and C_c is too short compared with that in compound **23** (4.2 versus 5.4 Å), and in compound **26** the distances between atoms C_a and C_b and between C_a and C_c are too long compared with those in compound **25**; hence compounds **24** and **26**, which have no ambergris character, do not contain the AAF.

The $L_{\alpha\beta}$ and $L_{\alpha\gamma}$ distances are also important in the Karanal isomers (**8a–8h**, Figure 8). All four active pairs of diastereoisomers (**8a–8d**) have a *cis*-configuration about the dioxane ring, with the cyclohexenyl substituent equatorial and the *sec*-butyl group axial. In this configuration, the distances between the β and γ carbon atoms of the *sec*-butyl group and the α methylene group of the cyclohexenyl group (i.e. $L_{\alpha\beta}$ and $L_{\alpha\gamma}$ respectively) satisfy the distance criteria of the AAF. However, in the *trans*-configuration these distances (L_{ab} and L_{ac}) become too long because of the equatorial position of the *sec*-butyl group and, as a consequence, the odourless isomers **8e–8h** no longer possess

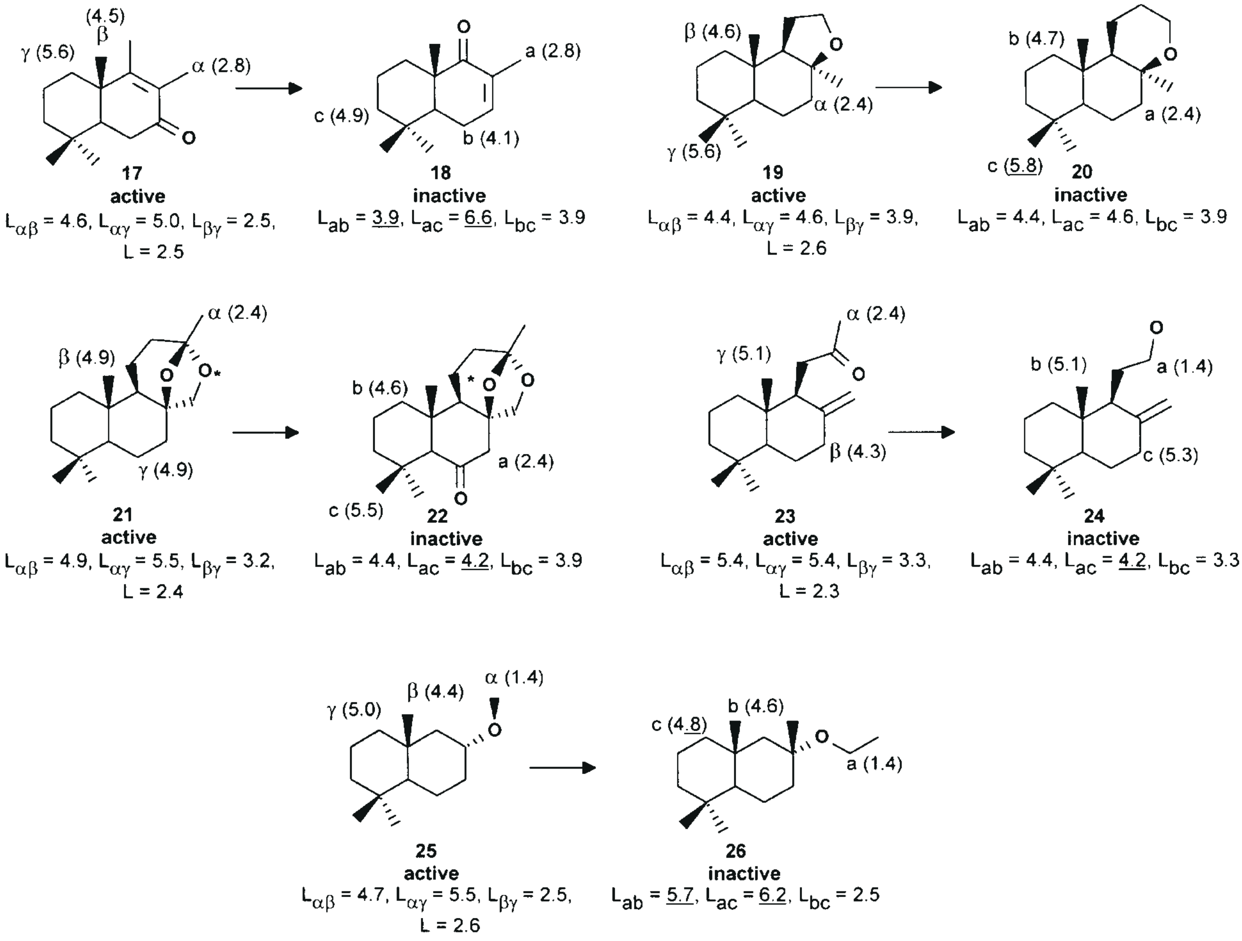
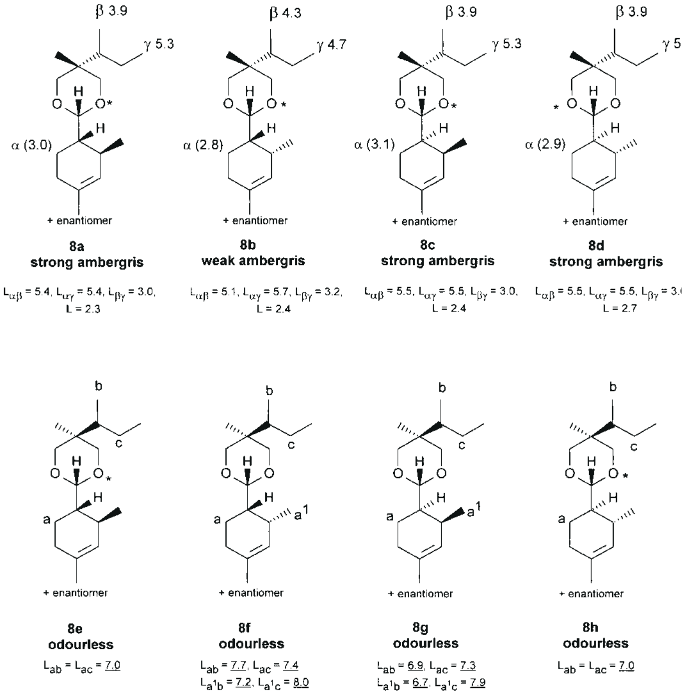


Figure 7 Structurally related active and inactive compounds which illustrate the importance of the AAF's distances. The distances which do not meet the AAF criteria in the inactive molecules are underlined. For polyoxygenated compounds the oxygen atom which is part of the AAF is marked by an asterisk. L is the distance between the Hα atom and one of the unshared electronic pairs of the AAF's oxygen atom.

the AAF. For the inactive isomers **8f** and **8g**, both oxygen atoms satisfy the requirements for the AAF, which in turn leads to two candidate alpha carbon atoms (a or a^1). However, neither of these fulfil the L_{ab} or L_{ac} criteria. In the case of the weak smelling ambergris stereoisomer (**8b**), molecular modelling shows that there are two low energy conformers which result from rotation about the bond joining the two cyclic systems. The lowest energy one (29.33 kcal/mol) is postulated to be inactive because the distance L_{ac} is too long, whereas the second one (**8b**, Figure 8, energy = 29.84 kcal/mol) meets all of the AAF's requirements. Since the energy barrier to rotation is relatively high (7.6 kcal/mol), the population of the active conformation (**8b**) will be low; this is consistent with the observation that **8b** only has a weak ambergris odour. It is worth pointing out here that, for flexible molecules, all possible low energy conformations need to be investigated to determine whether or not the molecule possesses the active ambergris fragment. For example, in the case of the active Karanal stereoisomer (**8c**), MM2 conformational analysis shows that rotation about the bond joining the two rings gives rise to three local energy minimum conformations of energies 29.39, 29.86 and 30.43 kcal/mol. Two of these satisfy the AAF's requirements; the one with an energy of 29.86 kcal/mol is shown in Figure 8. The conformation which does not possess the AAF is, in fact, the lowest energy one.

It is generally accepted that the conformation of a molecule responsible for triggering an odour response does not necessarily have to correspond to any of the theoretical minimum energy conformations. This phenomenon is also well accepted in drug–receptor interactions. Burgen *et al.* (1975) suggest that when a flexible drug molecule binds to a receptor, it is probable that a nucleation complex is first formed by association of part of the drug with a subset on the receptor. The half-life of dissociation at this subset is long enough to allow conformational rearrangement of the drug molecule favouring binding at subsites. Hence the need for thorough conformational analysis in all structure–activity relationship (SAR) work.

The examples which we have discussed so far have



+ enantiomer

8a
strong ambergris
$L_{\alpha\beta} = 5.4$, $L_{\alpha\gamma} = 5.4$, $L_{\beta\gamma} = 3.0$, $L = 2.3$

8b
weak ambergris
$L_{\alpha\beta} = 5.1$, $L_{\alpha\gamma} = 5.7$, $L_{\beta\gamma} = 3.2$, $L = 2.4$

8c
strong ambergris
$L_{\alpha\beta} = 5.5$, $L_{\alpha\gamma} = 5.5$, $L_{\beta\gamma} = 3.0$, $L = 2.4$

8d
strong ambergris
$L_{\alpha\beta} = 5.5$, $L_{\alpha\gamma} = 5.5$, $L_{\beta\gamma} = 3.$ $L = 2.7$

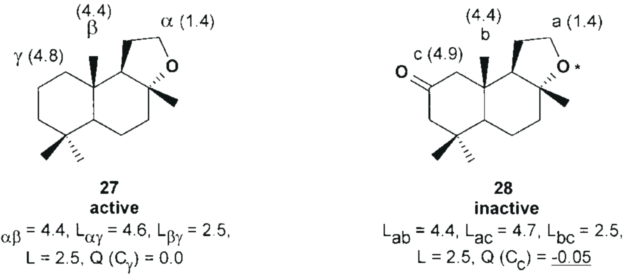
8e
odourless
$L_{ab} = L_{ac} = \underline{7.0}$

8f
odourless
$L_{ab} = \underline{7.7}$, $L_{ac} = \underline{7.4}$
$L_{a^1b} = \underline{7.2}$, $L_{a^1c} = \underline{8.0}$

8g
odourless
$L_{ab} = \underline{6.9}$, $L_{ac} = \underline{7.3}$
$L_{a^1b} = \underline{6.7}$, $L_{a^1c} = \underline{7.9}$

8h
odourless
$L_{ab} = L_{ac} = \underline{7.0}$

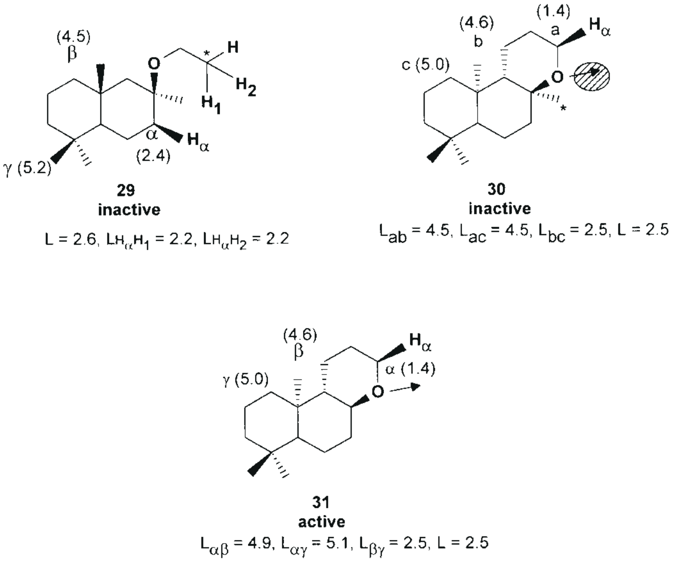
Figure 8 Application of the active ambergris fragment (AAF) distance rules to the Karanal isomers. The distances which do not meet the AAF criteria are underlined. In isomers **8f** and **8g** there are two candidate α carbon atoms (a or a^1).



27
active
$L_{\alpha\beta} = 4.4$, $L_{\alpha\gamma} = 4.6$, $L_{\beta\gamma} = 2.5$,
$L = 2.5$, $Q\,(C_\gamma) = 0.0$

28
inactive
$L_{ab} = 4.4$, $L_{ac} = 4.7$, $L_{bc} = 2.5$,
$L = 2.5$, $Q\,(C_c) = \underline{-0.05}$

Figure 9 Compounds **27** and **28** highlight the importance of the electronic characteristics of the active ambergris fragment. Q is the effective atomic charge in Hartree's atomic units, which for compound **28** falls outside the required range of –0.04 to 0.16 a.u.



29
inactive
$L = 2.6$, $L_{H_\alpha H_1} = 2.2$, $L_{H_\alpha H_2} = 2.2$

30
inactive
$L_{ab} = 4.5$, $L_{ac} = 4.5$, $L_{bc} = 2.5$, $L = 2.5$

31
active
$L_{\alpha\beta} = 4.9$, $L_{\alpha\gamma} = 5.1$, $L_{\beta\gamma} = 2.5$, $L = 2.5$

Figure 10 Importance of steric accessibility of Hα atom and the oxygen atom's active electronic pair (AEP). In compounds **29** and **30**, the Hα and the AEP respectively are sterically shielded by the methyl group marked by an asterisk. In compound **31** the methyl group has been replaced by a hydrogen atom and hence the steric shielding of the AEP has been reduced.

illustrated how structural modifications which alter the AAF's distances give rise to compounds which no longer possess an ambergris odour. Let us now turn to the remaining requirements of the active ambergris fragment: the atomic charges of the oxygen atom, C_α, C_β and C_γ; the steric accessibility of the H_α atom; and the steric accessibility of oxygen atoms' active electronic pair (AEP).

The active and inactive compounds, **27** and **28** respectively (Figure 9), highlight the importance of the AAF's electronic characteristics. Although both compounds fulfil all of the other requirements for the active ambergris fragment, only compound 27 has the correct atomic charge on the C_γ atom (0.0). In the inactive compound (**28**), the charge (Q) is –0.05 a.u., which just falls outside the required range of –0.04 to 0.16 a.u.

In compounds **29** and **30** (Figure 10), the H_α atom and the AEP respectively are sterically shielded by a methyl group; thus, although both of these compounds meet the other requirements of the AAF, they do not possess a strong ambergris odour. Compound **29** has a weak anisic and medicinal odour (Winter, 1989) and compound **30**, to those who can smell it, has a very weak ambergris odour (Ohloff *et al.*, 1980). Twelve out of the 30 subjects who assessed compound **30** as a 1% ethanolic solution from a smelling strip could not detect an odour. All of the remaining subjects perceived it as weak and ambergris, except for one female who described it as strongly camphoraceous, slightly sweaty and urine-like. Replacing the methyl group adjacent to the ether oxygen atom by a hydrogen reduces the steric shielding of the oxygen atom's active electronic pair and, as a result, compound **31**, which is a strong ambergris odorant, completely satisfies the AAF's requirements.

Summary

The electronic–topological approach has been used to define an AAF which correctly describes the presence (or absence) of the ambergris odour of all 181 compounds investigated. The AAF consists of one oxygen atom and three carbon atoms (α, β, γ) which are separated by certain key distances and which possess certain atomic charges. The C_α atom must bear at least one hydrogen atom (H_α), which is located at a certain distance from one of the unshared electronic pairs of the oxygen atom.

This investigation into the relationship between structure and ambergris odour has used the largest data set of closely related active and inactive compounds to date, and has included several non-*trans*-decalin examples, such as the ambergris-smelling and odourless diastereoisomers of the aroma chemical registered under the tradename of Karanal. The development of structure–activity relationships is an iterative process. The AAF will be used to aid the design of novel ambergris molecules and the results from this work used to further refine the model if exceptions to the rules are found.

In all structure–odour relationship work, the greatest potential for error is undoubtedly the organoleptic data. In order to investigate a large number of compounds we have used data obtained both by ourselves and by other workers. Care must always be taken when combining odour data from different sources. Discrepancies between reported odour characteristics for the same compound are not uncommon. Factors contributing towards these discrepancies include the absence of a universal odour language, the subjective nature of odour perception, different methods of sensory assessment and the presence of trace impurities. Many materials which smell of ambergris also have some woody or animal character and vice versa. The presence of more than one olfactory note may stem from the presence of isomers (Ohmoto, 1991); for flexible molecules, from the detection of different conformers; or simply just subjectivity (Schulte-Elte *et al.*, 1991). Many ambergris odorants also provoke specific anosmia, that is, either the inability to smell a particular odorant or a dramatically reduced sensitivity to that odorant. The phenomenon of anosmia can, for example, lead to the same compound being described by one person (who is prone to 'ambergris' anosmia) as purely woody and by another (who is prone to 'woody' anosmia) as purely ambergris. This highlights the need to use, wherever possible, an expert panel and a standard glossary of descriptors to minimize the problems associated with subjectivity. Despite these drawbacks, the ambergris family is one of the most suited odour types for structure–odour relationship studies because its odour is one of the least difficult to define and many molecules belonging to this family are relatively rigid. The next challenge is not only to be able to classify molecules into those which have an ambergris odour and those which do not, but to be able to predict the intensity of the active ones and to account for differences between the organoleptic properties of optical isomers.

Chemists are always tempted to interpret their observations on SARs in mechanistic terms and to postulate ways by which biological activity could be brought about by some feature of molecular structure or chemical activity that seems significant in the SAR. It is also tempting to do the reverse, that is, to postulate a biological mechanism and then work backwards to structural features that might satisfy it. Despite the significant advances made over the past decade in the biochemistry of olfaction, our understanding of the mechanism of odour perception is still rather limited (reviewed in Sell, 1997). However, SAR can be a useful tool in the design of new odorants.

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