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Chemistry of odor stimuli

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Summary. The present state of the molecular basis of olfaction is shown. With the aid of various examples the regioselectivity of odor sensation is proven. The main part of the experimentation concerns the stereocontrolled process of odor release.

Key words. Olfaction; odorants; structure-activity relationships; stereospecificity.

Odorant recognition process

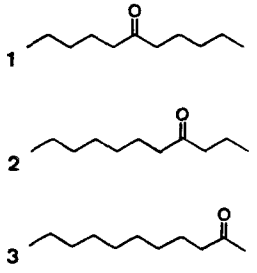
Since Ottoson's decisive experiments[59] olfaction is considered to be a bimolecular process involving the interaction of an airborne molecule with a complementary site of a receptor system which takes place at the interfaces of peripheral nerve cells located within the mucous layer of the olfactory epithelium. The induced intramolecular results in the formation of a reversible non-covalent complex giving rise to cell-depolarization, triggering the receptor potential in the sensory neurons. Membrane proteines can serve as olfactory receptors in mammals[36]. There is strong evidence, that cyclic AMP function as a second messenger in olfactory transduction[60]. The generated impulse discharge encodes the strong reponse and signal a pattern to the brain's olfactory center which already provides all information about the molecular properties of the ligand and in particular about the biochemical nature of the neuro-active complex. The resulting output signal is analyzed in the brain and then confronted with stored-up recognition patterns. The final outcome of this still incompletely understood cascade of biochemical and neurophysiological reactions, which can be as brief as 300–400 ms[33] is the ability to perceive and describe both the quality and strength of an odor. Even so the process of information is not yet finished. Olfactory neural signals can pass from the olfactory bulb to other parts of the central nervous system. It is through these further connections that the olfactory process affect overall brain functioning including learning and memory, sexual behavior and emotional regulation in men.

Molecular criteria for olfactory compounds

The physical and chemical properties required of a suitable stimulant molecule are determined by the location, molecular architecture and physiological medium of the chemoreceptor. It is evident that sensory activity is exclusively associated with volatile molecules. The highest molecular weight found so far for an odorant is 294[18]. Chemical reactivity of a ligand has little if any direct connection with olfactory activity since odorant molecules are uncharged and not associated with metabolic biochemical transformation. Nevertheless, several molecular requirements must be met. Thus it is evident that odorous molecules always contain both a strong hydrophobic and a relatively weak polar region. The latter, usually termed the 'osmophore'[69], is associated with a functional group such as carbonyl, hydroxyl, occasionally an ether or a limited variety of heteroatomic homologues. However, the presence of a functional group is not a *conditio sine qua non* for receptor interaction. Even alkanes can have distinctive odors.

Regioselectivity in molecular olfaction

Although changes in sensory activity associated with small and gradual changes in molecular structure have been intriguing scientists active in a number of disciplines for at least 30 years, no major breakthrough has been made so far in the quantitative or qualitative correlation of these changes[7]. All we know today is that the olfactory character of an organic compound is somehow a function of the spatial arrangement of the molecule, and that it is further influenced by its electronic and hydrophobic properties. Here the immediate molecular environment of the osmophoric group appears to play an important role, as impressively demonstrated by v. Braun and



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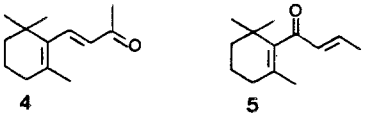
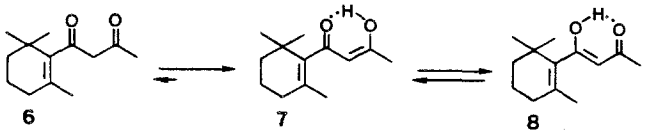
Kröper[9] in the case of a very simple model compound: Symmetrical 6-undecanone (**1**) has a pronounced fruity odor which changes almost systematically as the symmetry of the molecule is changed by altering the position of the carbonyl group. 2-Undecanone (**3**) prossesses the distinctively different odor of oil of *Ruta graveolens* L. (ruewort)[80] while the ketone with the carbonyl group in the intermediary 4-position (**2**) has an odor which combines the qualitative characteristics of both.

A simple transposition of the osmophore can lead to a drastic change in odoriferous properties. β-Ionone (**4**) has the characteristic fragrance of violets, whereas *β*-damascone (**5**)[17] in equal concentration exhibits a completely different and complicated odor profile in which fruity-flowery, exotic-spicy and chrysanthemum-like elements predominate.



4 **5**



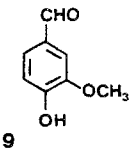
6 **7** **8**

The diketone **6**[76] is mainly present as a tautomeric equilibrium between the two enol forms **7** and **8**[66] and thus combines the functional structural elements of **4** and **5**: this situation is reflected in its sensory properties, as the odor qualities of both ketones **4** and **5** appear simultaneously. The enone moiety of 7-hydroxy-*β*-ionone (**8**) adopts the cisoid conformation because of the strong hydrogen bridge, whereas *β*-ionone (**4**) in solution certainly prefers the transoid conformation, which does not seem to have any important olfactive consequences.

In vivo studies have localized Schiff base forming proteins in the olfactory epithelium of experimental animals which can provoke a selective anosmia[36]. These findings may suggest the existence of carbonyl group recognizing substructures of ligands at specific sites. Even an analogy of the transduction mechanism between olfaction and vision has been envisaged. As well as a covalent complex of ll-cis-retinal and the protein opsin dipolarizes rod cells in the retina carbonyl group containing odorants may stimulate olfactory receptors in a similar way[37].

Functional groups play a particular role in the odor release of benzenoid ligands, the directed dipole-dipole interaction being the main driving force in the receptor event. This principle of molecular oriented profiles[7b] is demonstrated by comparing vanillin (**9**) with the practically odorless isovanillin (**10**).

Shifting the secondary methyl group adjacent to the oxygen function in the commercially important isochroman musk Galaxolide® (**11**)[7c] to the position shown in **12** alters the direction of the vector and magnitude of the dipole moment, resulting in the loss of odor. The substitution of the methyl group in Tonalide® (**13**) by an isopropyl group **14** prevents the coplanarity of the carbonyl group with the benzene ring and is sufficient to make the strong musk-like odor disappear completely[12].



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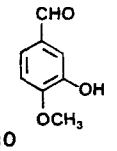

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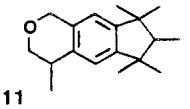

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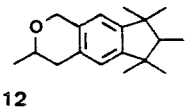

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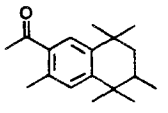

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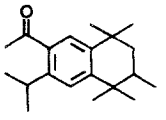

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The dipole moment cannot be only prerequisite for a successful receptor interaction. Benzene and naphthalene both ($\mu = 0$ D) have a strong and particular odor. Hydrophobic cavities forming a Stetter complex[77] or a sandwich arrangement of two appropriate receptor molecules with one aromatic ligand have been demonstrated in model reactions[29], and these might be responsible for the odor release.

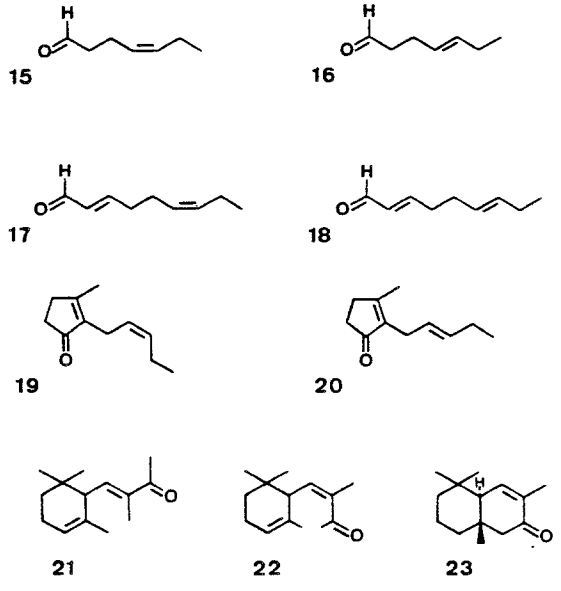
Correlation of stereochemistry and sensory activity

In analogy to Emil Fischer's 'lock-and-key' theory of enzyme-substrate interaction leading to functional complexes Linus Pauling has suggested that the size and shape of a molecule is responsible for its physiological activity[61]. This is the basis of Amoore's 'Stereochemical Theory of Odor'[3] which in a modified version presumes that olfactory substances which can cause an 'anosmic defect' interact with specific receptor sites and lead to the production of so-called primary odors[4]. The shadow-matching method for the measurement of morphological similarities[5] between odor types can be carried out today by computer-assisted molecular surface analysis with graphical display[35]. More recent work[13] has dealt with the importance of 'volume' and 'bulk' parameters in arriving at quantitative structure-activity relationships (QSAR). A QSAR study of monocyclic nitro-musk odorants using pattern recognition analysis and feature selection yielded two different sets of 13 molecular structure descriptors allowing the prediction of novel musk odorants and non-musk compounds[26]. Space-filling models in terms of charge density maps established by semi-empirical molecular orbital calculations CNDO[7,25,65] have been investigated with odors of pyridines[21] and in the case of bitter almond smell[34]. Allinger's approach concerning the quantitative comparison of molecular shape and interactive site orientations[1] has been questioned by others[38]. We agree with Hansch[27] that the purely physico-chemical approach of evaluating a possible 'steric effect' in the biological activity of a molecule may well lead to an over-simplification in trying to explain the true nature of its interaction at a macromolecular surface. In the following we shall attempt to examine the connection between olfactory perception and the stereochemistry of a stimulant molecule.

Geometry-dependent odor release of unsaturated carbonyl compounds

Oxygen-containing n-alkenes belong to the most widely distributed aroma components, the *Z*-isomers of which being perceived as more 'natural' and also more pleasant. At very low concentrations (1 ppb) (*Z*)-4-heptenal (**15**) has a creamy butter flavor[28], whereas the *E*-isomer **16** has an aggressive putty and green odor[39] reminiscent of the saturated heptanal. (*E*,*Z*)-2,6-Nonadienal (**17**) contributes decisively to the odoriferous principle of cucumber flavor as well as violet leaf oil[46]. The odor of (*E*,*E*)-2,6-nonadienal (**18**) however is different from **17** and has been associated with the fatty tallowy cucumber flavor in beef and mutton tallow. An exact odor description for one of the most important jasmine odorants has been given:[16] 'The odor of *cis*-jasmone (**19**), although of similar type to that of *trans*-jasmone (**20**), has an exotic subtlety which the latter does not possess. Synthetic dihydrojasmone is used as a substitute for natural jasmone but in our opinion is distinctly inferior to *cis*-jasmone (**19**).'[15]

The examples **15**–**20** show that the geometry of an alicyclic double bond only marginally influences tonality and odor strength. Because of the similarity of their molecular profiles the odor properties of the dihydro derivatives are more related to the (*E*)- than to the (*Z*)-isomer. We suppose that all three types of compounds ((*Z*)-, (*E*)- and saturated derivatives) can be recognized by the same active site, but the odor nuances occur owing to slightly deformed architecture of the neuroactive complex. A different result is obtained for compounds **21** and **22**. (*E*)-8-Methyl-α-ionone (**21**) has been known as an artificial violet odor in the perfume industry for about 80 years. However, the odor changes considerably after an isomeric change of the double bond. (*Z*)-8-Methyl-α-ionone (**22**) loses the flowery odor, becoming a pleasant and strong woody, tobacco-like note[23] resembling that of the bicyclic ketone **23**. For this reason it can be supposed that on odor perception of **21** and **22** there are two different receptor incidents, whereby **22** assumes a conformation similar to **23**.



Diastereoselectivity of odor sensation. Mutation of camphoraceous to sandalwood odor by change in stereochemistry.

According to Amoore's 'stereochemical' theory, camphoraceous primary odor occurs when a spherical ligand of moderate molecular size[2,3] meets a cup-shaped receptor site. With the aid of the shape factor, molar volume and other physicochemical parameters the camphoraceous odor of non-spherical molecules can also be predicted[20]. There are indications that the camphor receptor, at least in rats, is a membrane protein with a molecular weight of approximately 120 000[22]. The camphoraceous stimulant does not necessarily carry functional groups, because the same odor can emanate from globular hydrocarbons. Neither diastereoselectivity nor even enantioselectivity are conditions for the odor, because 2-methylborneol (**24**) and 2-methylisoborneol (**25**) or their antipodes exhibit the same camphoraceous odor[62,81]. Lack of enantioselectivity in odor perception has also been observed for campher, the principle compound associated with camphoraceous odor[79].

With an increasing number of carbon atoms in the side chain, the stereochemistry of the bulky part starts to be differentiated, regardless of which part of the molecule the functional group is situated. In the ideal case a sandalwood odor is produced. Representative for a large number of examples[10,11,43] are β-santalene hydrate **26** and its epimer **27**, as well as (+)-β-santalol (**28**) and (+)-epi-β-santalol (**29**). Whereas the compounds with the 3-*exo* side chain, **26** and **28**, possess the distinct and strong odor of sandalwood oil, the faint woody odor of the 3-epi-derivatives **27** and **29** only vaguely recalls the essential oil[75].

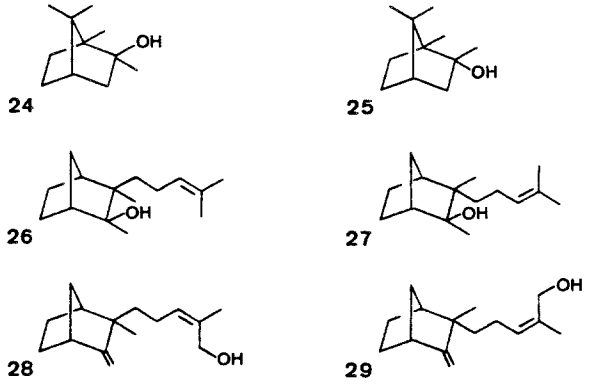


Figure 1. Camphoraceous compounds (**24** and **25**) versus typical sandalwood odorants (**26** and **28**).

The bifunctional unit concept

Hydroxy carbonyl compounds based on the *p*-menthane skeleton, such as compounds **30**–**37**, can exhibit a strong flowery fragrance provided the distance between the functional groups is as small as possible without their being subject to internal hydrogen bonding[50]. Compounds **30** and **34** are odorless, whereas hydroxy-aldehyde **31** in contrast to its diastereomer **35** has an odor resembling lily of the valley. In the series **34**–**37** where the hydroxy group is *trans* to the methyl group and *cis* to the

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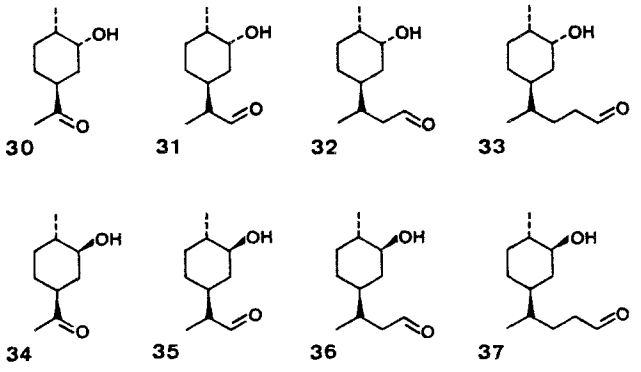
carbonyl-bearing chain **37** exhibits a noticeable odor. Remarkably, the odors of compounds **31**, **32**, **33**, and **37** are almost indistinguishable.



Examination of molecular models shows that the axial hydroxy group in **31a** is 2.3 Å distant from the aldehyde carbonyl whereas in its diastereomer **35a** the corresponding distance is 4.4 Å (fig. 2). On approaching a receptor surface these functional groups will meet with corresponding proton-donor (AH) and proton-acceptor (B) sites which usually are 3 Å distant from each other. **31a** illustrates this encounter by means of a three-point binding model. If requisite distances are exceeded then, in the most favorable case, only a two-point interaction (**35a**) will result, and this apparently is insufficient to produce a specific odor.

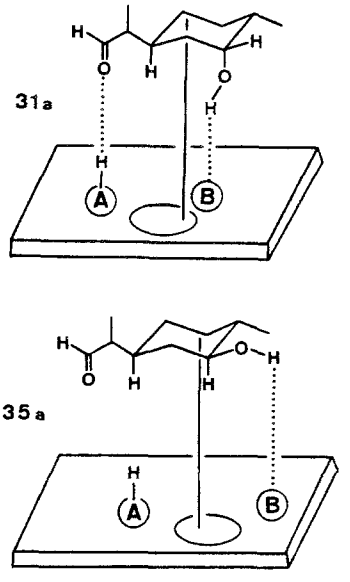
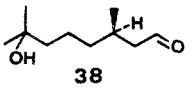


Figure 2. **31a**: Three-point binding of (+)-(2*RS*,1′*S*,3′*R*,4′*S*)-2-(3′-hydroxy-4′-methylcyclohexyl)propanal.
35a: Two-point 'interaction' of (+)-(2*RS*,1′*S*,3′*S*,4′*S*)-2-(3′-hydroxy-4′methylcyclohexyl)propanal.

(+)-(3*R*)-7-Hydroxy-3,7-dimethyloctanal (**38**), the prototype for the sweet-floral odor resembling lily of the valley[6], was the first commercially available bifunctional odorant, in 1908, under the trade name Cyclosia®. As yet the 'active' conformation of **38** during complexation with the receptor molecule is unknown. Most probably it involves a three-point interaction of a coiled conformation.



Caramel-like flavor impression (fig. 3) is produced by a three-point interaction with similar molecular features as the totally different flowery odor of figure 2. However in the case of caramel odor the strong hydrogen bond of a planar alkyl-enol-carbonyl substructure present in cyclic dicarbonyl compounds is required[30] (fig. 3). The fact that the odor strength increases if a methyl group is substituted by an ethyl group indicates the latter's ideal occupation of the hydrophobic pocket in the cavity of the

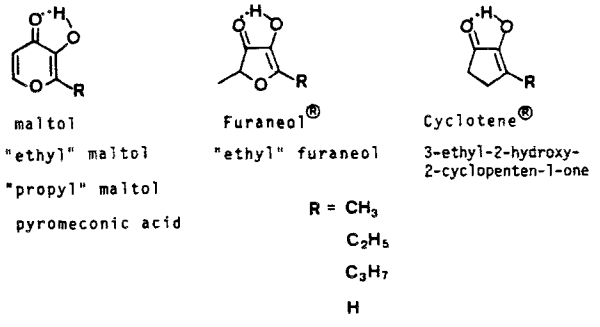


Figure 3. Character impact aroma compounds of caramel flavor.

active site. Indeed 'ethyl' maltol is about five times stronger than maltol, 'propyl' maltol has much less and pyromeconic acid no receptor activity whatsoever[48] (fig. 4).

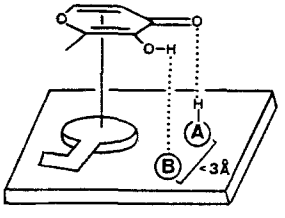


Figure 4. Specific receptor interaction of maltol. Three point-binding model.

Organic chemistry boasts an almost unlimited number of bifunctional compounds which possess both an H-donor and H-acceptor group, a certain number of which have been examined with regard to a structure-odor relationship[48]. Benzenoid bifunctional derivatives of the salicylic and anthranilic type (fig. 5) occurring in flavors, essential

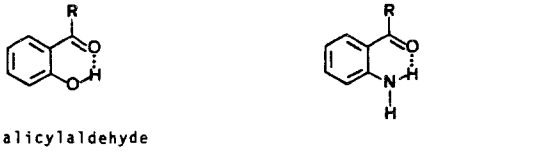


Figure 5. Salicylic- and anthranilic-type odorants.

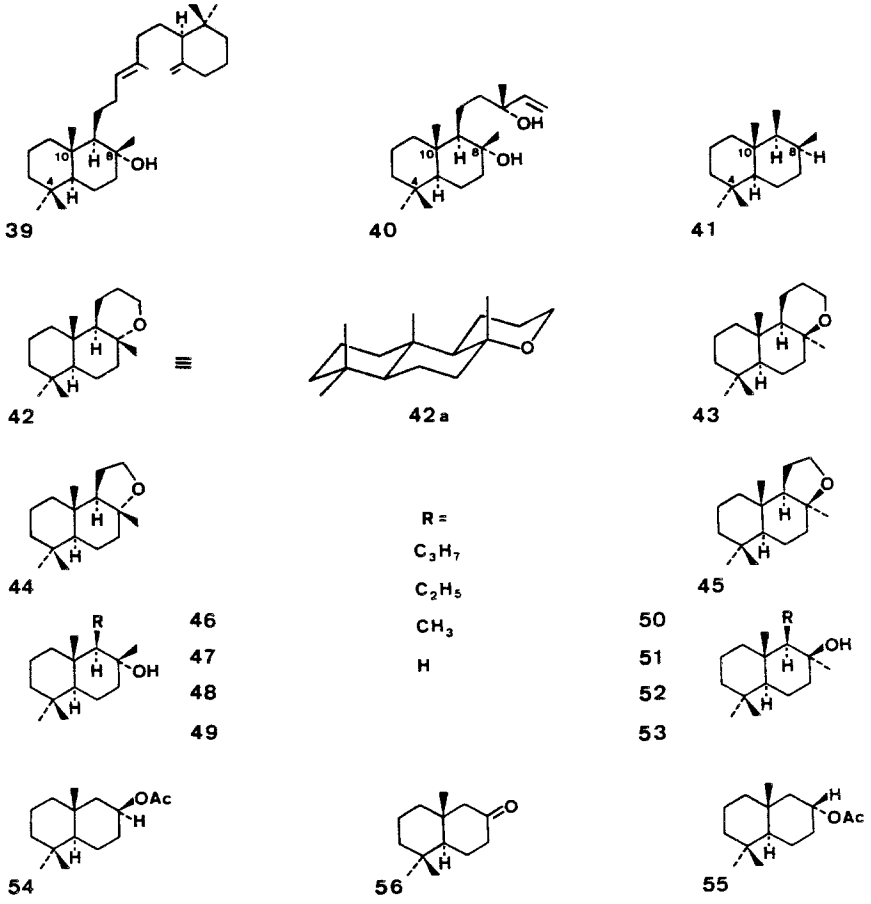
oils, resins and other natural materials are presented as representative examples. Depending on the heteroatom of the bifunctional units which form a strong intramolecular H–bond and the nature and/or degree of substitution of the 6 π-electron system different sensory activity can be caused. The consequence of these modification is the great variety of odor impressions, the most frequent of them being: floral, spicy, fruity, smoke-like, leathery-phenolic, animal and oakmossy.

In addition this class of odorants shows unique link to taste compounds. Indeed, the interaction between a sweetener and its receptor molecule requires complementary proton-donor (AH) and proton-acceptor (B) groups which form an intramolecular hydrogen bonding system[19,71]; an apolar area in the sweetener is important for efficient binding[32].

Triaxial rule of odor sensation

Ambrein (**39**), a triterpene alcohol found exclusively in ambergris, the large number of known diterpenes based on the labdane skeleton (**40**), and the relatively small number of sesquiterpenes based on the drimane system (**41**) all have in common a *trans*-decalin nucleus with the same absolute configuration[44,49]. Degradation of the side chain attached at C_9 in ambrein (**39**) and sclareol (**40**) leads to well-known ambergris-type fragrances, provided that the stereochemistry of the *trans*-decalin is left unchanged, an oxygen function remains and the degradation leads to a carbon skeleton of not less than 13 and not more than 18 carbon atoms[49]. A prototype (in odor tonality and intensity) of this group is the tricyclic ether (–)-deoxyambreinolide (**42**)[70], which is a typical degradation product of (–)-ambrein (**39**). In (+)-deoxyisoambreinolide (**43**) the chiral center at C_8 is inverted and this compound is odorless[58]. The lower homologue, the tricyclic ether (–)-Ambrox® (**44**), is accessible by oxidative degradation of (–)-sclareol (**40**), abundantely found in *Salvia sclarea* L.[78]. Ether **44** has both identical odor and absolute stereochemistry with its higher homologue (**42**) and is at present the most important ambergris-type fragrance used in perfumery. Here, a change of the stereochemistry at C_8, *i.e.* **45**, does not have such a dramatic consequence, as observed for **42** and **43**. (+)-Isoambrox (**45**) still has about 1% of the odor intensity of (–)-Ambrox® (**44**) according to its detection threshold data[52].

Opening of the tetrahydrofuran ring in compounds **44** and **45** leads to the series **46–53** where once again we encounter an 'all or nothing' situation. More precisely, in the alcohols **46–49** with the 'natural' configuration we recognize some aspects of the odor profile of ambergris, whereas their diastereoisomers **50–53** are odorless[51]. Acetate **54**, known as Polywood®, is the simplest known fragrance of woody-like ambergris-type and its diastereomer (**55**) is odorless. In (+)-5,5,9-trimethyl-*trans*-2-decalone (**56**) a prochiral carbonyl group appears to play the same role as the axial substituent at chiral C_8 since it, too, has an odor with ambergris-type characteristics[54].



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A large number of compounds which have been obtained by structural modification of compounds **42–56** provide further information about the relationship between sensory activity and possible interaction with a complementary receptor system. In fact, we can now arrive at a fairly accurate description of how ambergris-type odor is based on molecular structure, as represented by models A and B (fig. 6). The odor of compounds of this type appears to be intimately connected with the *trans*-decalin skeleton (A), none of them being based on *cis*-decalin (B). Here we consider that the multi-point interaction between the stimulant molecule and the complementary receptor site requires an axial configuration for substituents R′, R″ and the β-substituent R_a in model A. The hydrophobic part of the interacting groups appears to be of primary importance. Oxygen functions can be attached at one of the critical positions (R′, R″, R_a or R_e). The diastereospecificity of the amber-type fragrance has been previously summarized in the form of a 'triaxial rule of odor sensation'[49,54] and extended to a number of decalin-based sesquiterpenes of which a large variety occur in essential oils[47].

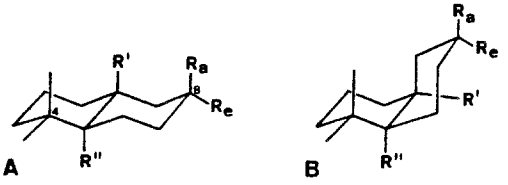
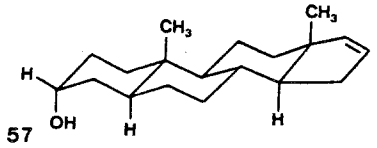
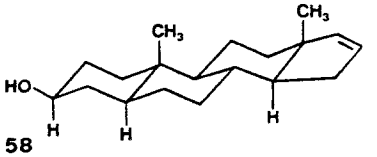
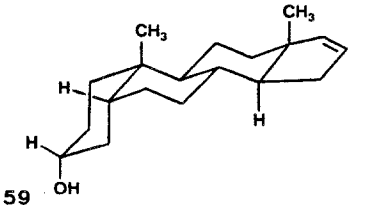


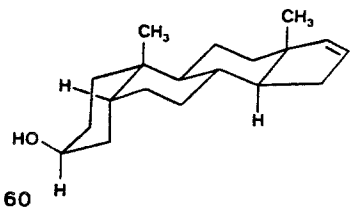
Figure 6. Triaxial rule of odor sensation. Schematic representation of the relationship between the decalin ring system and ambergris odor[49].

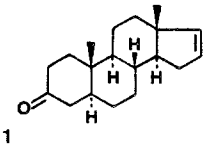
Odoriferous steroids, can also be considered in the light of the 'triaxial rule'[44,57], especially in view of the fact that the stereochemistry of rings A and B having been indicated as being chiefly responsible for specific odor release[64]. 5α-Androst-16-en-3α-ol (**57**) has a strong and long lasting musk-type odor, whereas its 3β-epimer **58** is odorless. The former was first isolated from hog testes[63], and both, together with ketone **61**, an odoriferous urine constituent, were then found in both urine and arm-pit

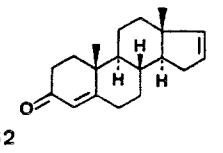








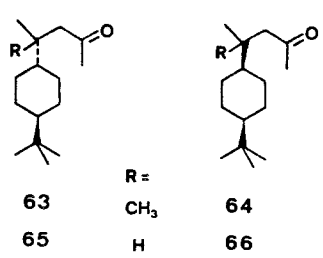




perspiration of human beings. These compounds have been considered as possible sexual chemical messangers, and there has even been talk of the 'likelihood of human pheromones'[14,40]. Furthermore the 3α-alcohol **57** and the corresponding ketone **61** have been identified as pheromones of sexually mature hogs; on the other hand the 3β-epimer **58** has been found to be devoid of any aphrodisiacal activity[67,72]. Alcohols **59** and **60**, with a *cis*-junction between rings A and B, appear to completely lack a characteristic odor altogether[64]. From the examination of about 50 such steroid derivatives a fairly comprehensive picture of the receptor activity of the 'steroid scent' has been obtained[57].

Conformational control of odor sensation

Structurally unrelated types of compounds may show similar odor characteristics, but, so far, on the basis of molecular structure, no satisfactory explanation for this phenomenon has yet been found[7]. A particularly remarkable example is that of the diastereoisomeric ketones **63** and **64**[8]. The *cis*-compound **64** possesses the same penetrating urine odor as the steroids **61** and **67**, while its *trans*-epimer **63** is odorless[79]. If one attempts to draw a parallel between the structures of the two ketones **63**/**64** and the corresponding steroid **67** on the basis of the size and shape of their molecular peripheries, one reaches the conclusion that it is compound **63** and not its epimer **64** which ought to exhibit a 'steroid-type' odor. The situation becomes yet more complicated as we consider the lower homologues **65** and **66**. Here it is the *trans*-epimer **65** which has an odor identical to the *cis*-compound **64**, and it is the *cis*-epimer **66** which is odorless[55].



One explanation is based on conformational considerations occasioned by the gem-dimethyl group. From force field calculations it can be deduced that it is only the nor-compound **65** which is able to assume an elongated

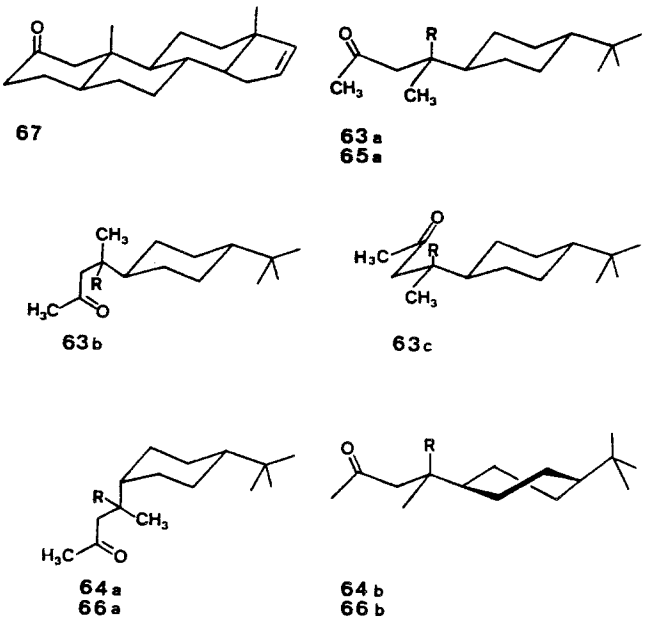


Figure 7. Conformers of stereoisomeric 4-(4′-*t*-butylcyclohexyl)4-methyl-2-pentanone (R = CH_3) and 4-(4′-*t*-butylcyclohexyl)-2-pentanone (R = H).

seco-steroidal conformation such as **65a** whereas its dimethyl homologue **63** prefers a bent-chain conformation such as **63b** or **63c**. For the *cis*-compound **64** a chair conformation such as **64a** is unlikely for reasons of steric hindrance, and most probably this compound exists in a twist form such as **64b** which would be more amenable to a steroid-like receptor. On the other hand, in the monomethyl analogue **66**, a chair conformation appears to be favored in which the side chain bearing a carbonyl group would be most likely to assume an axial conformation and thus result in a non steroidal shape such as **66a**[55]. Ketones **63–66** are the first examples in the history of olfaction where conformational analysis has been used to predict specific odor release without any information on the molecular characteristics of the active site within the sensory nerve cell membrane.

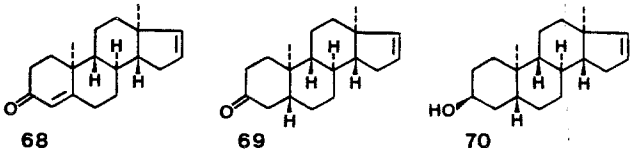
Enantioselectivity of odor perception

It is a well established fact that the biological activity of many substances depends largely on their chirality. (+)-Estrone is the active estrogenic hormone whereas its enantiomer has no activity at all. (*S*)-Asparagine has a bitter taste, the (*R*)-enantiomer is sweet. Chiral recognition has been found in olfactory insect communication[73], where the 'wrong' enantiomer can cause an inhibitory effect. Chiral discrimination has been found to take place in different olfactory cells of the antenna, the optical antipodes of 4-methylhexanoic acid[31] and ipsdienol[41] are representative examples.

The fact that the human nose is able to distinguish with varying success between enantiomers has been documented in a number of cases (see literature cited in ref.[58]). Enantiospecific routes to both antipodes have been successfully followed from a single progenitor in the case of the following well known odorants: citronellol[68], linalool[56], carvone[24], rose oxide[45], 7-hydroxydihydrocitronellal (**38**)[74], nerol oxide[53] and patchouli alcohol[42]. In all cases the odor quality and strength of the enantiomers were found to be different.

From the accumulated results concerning the close relationship between stereochemistry and sensory activity we would have expected a high enantioselectivity of odor perception for those substances which follow the triaxial rule. Indeed, (+)-deoxy-isoambreinolide (**43**) is reported as to be odorless, whereas its enantiomer could be perceived[58]. However, nobody indicated the typical properties of ambergris odor. The 'wrong' answers much more resemble those from people with anosmic defects when questioned about odorants related to the triaxial rule.

(+)-Androsta-4,16-dien-3-one (**62**) has been known as having a pronounced urine odor[64], with a very low threshold concentration of 1 ppb[57]. When its 'unnatural' enantiomer **68** was submitted for testing to 40 people, none of them was able to detect an odor of any kind[47,55]. Of the panel, 75% were likewise unable to detect any odor when confronted with the unnatural enantiomeric ketone **69** and alcohol **70**. The remaining 25% ascribed to ketone **69** a very weak urine musk type odor, whose lower threshold value was estimated to be 10^6 higher than that of the 'natural' epimer **61** (0.62 ppb[57]), and an exceedingly weak musk odor to alcohol **70**.



Conclusion

The following aphorisms are not to be understood as a theoretical interpretation (which is not allowed by the actual state of the art) of odor perception *per se*; they are just conceptions of the molecular interaction of stimulants with the chemoreceptor, based on experiments. Every new result can complete this 'list' or replace it. We need a pragmatical approach to overcome the rigid barriers given by the current 'theories' of olfaction.

– Odorants present a distinct structure-activity relationship. Small structure modifications can influence decisively the odor quality and strength. This fact shows that olfaction is a receptor event.

– The recognition process leads in the initial step to a reversible neuroactive complex between the odorant and the receptor molecule.

– In order to complex the substrate, the receptor molecule must possess a complementary stereoelectronic arrangement of binding sites and steric barriers.

– Ground-state complexation of odorants requires a high structural organization which is produced only through multiple site binding.

– The intermolecular interaction in olfaction involves: electrostatic attraction; hydrophobic bonding; van der Waals forces; hydrogen bonding; dipole-dipole interaction.

– Hydrophobic interactions are a major driving force for substrate binding in olfaction.

– Weak odorant binding means that the electrons in sensory active molecules are in the ground state. Indeed

odorants are almost always neutral molecules. Charged ligands are not yet known.

– There is strong evidence that no single molecular property is sufficient to determine the odor of a molecule. Odor quality is multidimensional.

– Substructural elements rather than functional groups have to be regarded as osmophores.

– The degree of selectivity will be translated in terms of odor quality. Odor strength is the expression of the binding force of the complex, determined by a multi-point attachment.

– The stereochemistry of a sensorily active compound can lead to a yes/no situation in olfaction. Diastereoselectivity, conformationally controlled odor perception and even total enantioselectivity has been observed.

– The chiral recognition of a substrate is based on a complementary interaction with a chiral binding site which gives rise of the formation of a reversible diastereotopic association.

– The high stereochemical control of the sensory process leads on to suppose that the active site is formed from protein substructures, capable of recognizing molecular features of an odoriferous substrate. Several odor qualities can be recognized from one and the same active site; a fact that has been used to demonstrate the 'triaxial rule' or the 'bifunctional unit concept'. The chemical nature of the neuro-active complex is decisive for the triggering of a specific smell; this complex would then change with each structurally modified ligand. These observations are in accord once with those of perfumers, who recognize a different smell with every sensorily active compound, no matter how small the nuances are.

Diversity and specificity of the olfactory system can be regarded as similar to that of the immune system. Recognition of odoriferous substrates by olfactory receptors resembles the detection of antigens by the immune system in which odorants behave like haptens.

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