Chem. Rev. **1996,** *96,* 3201–3240

Structure–Odor Relationships

Karen J. Rossiter

Quest International, Ashford, Kent, England, TN24 0LT

Received May 11, 1996 (Revised Manuscript Received September 9, 1996)

Contents

I. Introduction

Olfactory research has long been challenged by such questions as the following:

(1) How do we recognize and discriminate between thousands of odors?

(2) Which molecular properties determine the smell of a compound?

(3) Why, in some cases, do compounds which are completely different in structure have similar odors?

(4) And conversely, why do compounds which are very similar in structure have dramatically different odors?

Karen J. Rossiter was born in Ashford, Kent, England, in 1964. She received her degree in chemistry from the Royal Society of Chemistry in 1990 and is presently doing a part-time Ph.D. into the relationship between chemical structure and odor. This work is sponsored by Quest International, one of the world leaders in the fragrance, flavor, and food ingredient industry, and is being carried out in collaboration with the University of Kent. She is also a member of the UK QSAR discussion group. Karen Rossiter has worked for 10 years as an organic chemist in the Research Department of the Fragrance Division of Quest International. She has been involved in both process development and the discovery of new fragrance ingredients and has had one commercially successful new aroma chemical, Karanal, named after her. Her current research interests are in structure–activity relationships and their use in the design of novel fragrance ingredients.

(5) How can our sense of smell respond to chemicals which we have never encountered before and do so in a way that enables us to describe and categorize the odor?

For a compound to be smelt by air-breathing animals it needs to be volatile at ambient temperature. As a consequence odorants are nonionic compounds with molecular weights of less than 300. They are usually hydrophobic organic compounds containing a limited number of functional groups. However, the presence of a functional group is not necessarily a prerequisite for odor. Even alkanes can have pronounced odors, two notable examples being 2,4,4-trimethylpentane and cyclooctane, which are both strongly camphoraceous. In aquatic animals the molecular criteria for odorants are quite different with water-soluble materials, such as amino acids, being among the best.

The introduction of synthetic fragrance ingredients produced a revolution in the use of perfumes. Until 100 years ago, perfumes were made entirely of natural products and as a consequence their use was restricted to the wealthy and mostly for personal use. Today, fragrances are used in a wide range of consumer goods from personal products such as soap, shampoo, and deodorants to household products such as detergents, household cleaners, and even bleaches.

S0009-2665(95)00068-9 CCC: $25.00

The estimated world consumption of fragrance compositions is valued at over 2800 million dollars and that of the synthetic fragrance ingredients (aroma chemicals) 1400 million dollars.[1] Perhaps the most significant turning point in the history of the industry was the launch, in 1921, of the famous perfume Chanel No 5. This was the first fine fragrance to use synthetic organic chemicals to produce unique fragrance aspects, and its immediate success led to a growing interest in synthetic perfumery materials. The potential advantages of synthetic ingredients are clear: cost, availability, consistency, stability, originality, and additional functionality (e.g. a fragrance ingredient which has a deodorant effect).

The fragrance chemist, using the guidelines mentioned above, can make a compound which is likely to be fragrant. However, what will it smell like and how intense will its smell be? In an attempt to predict such properties, chemists have been searching for correlations between molecular structure and odor for more than six decades. The fruits of this research are a wide and varied collection of postulated structure–odor relationships (SORs).

This review provides a comprehensive summary of the published work in this area from its beginnings around 1930 to the present. It is organized alphabetically according to the different odor types rather than the correlation techniques applied. Earlier reviews tend to be of a fragmentary nature and cover either a limited number of odor types, usually the most extensively studied areas such as musk, ambergris, and sandalwood, or odor areas which have been examined by the authors in question.[2–5] I have extended the coverage to include, for example, bitter almond, camphor, jasmine, lily of the valley, rose, fruit, green, patchouli, and cedarwood. Within each odor area there are trends in the SOR techniques employed. In some cases, these are restricted to empirical rules or regression equations relating odor intensity or similarity to a few simple descriptors. In other odor areas the studies have been extended to include more modern approaches. Advances in theoretical and computational chemistry, coupled with the introduction of computer graphics, have made conformational analysis easier and allowed visualisation of molecules in 3-D. This has led to an increase in the number of postulated "osmophores", which are usually expressed as distance criteria between key structural fragments. Simultaneously, more powerful computers have allowed the rapid calculation of a wide range of molecular descriptors and provided improved data handling. This is reflected in the publication of odor-discriminating models derived from statistical techniques such as pattern recognition and, more recently, neural networks. At the first mention of each structure–activity relationship (SAR) technique, a few explanatory sentences will be included for the benefit of those readers with no detailed knowledge of SAR approaches.

The current rapid development of more sophisticated SAR techniques, particularly in the arena of drug design, is having a major impact on analogous research in the field of olfaction. The result is a prolific number of SOR publications. Particular attention will be given to recent publications which have not been included in any other previous review.

There are two unique problems in the application of SAR to odor. The first of these is an incomplete understanding of the mechanism of olfaction. Prior to the early 1980s the biochemical study of olfaction had been virtually neglected. However, over the past 15 years a great deal of information has been gathered on olfactory receptors and signal transduction, which has provided us with some initial insights into the biochemistry of odor perception. Current research activities in this area are likely to lead to an increase in our, presently rather limited, understanding of the olfactory system, which in turn should make the search for correlations between structure and odor easier. A summary of the biochemical study of olfaction is included as an introductory section to provide the reader with background information relevant to the topic of this review—the relationship between chemical structure and perceived odor.

The second unique feature of structure–odor relationship work is the difficulty associated with odor measurement. This difficulty arises from the subjectivity of odor, the dependence of odor quality and character on concentration, and the importance of organoleptic purity as opposed to chemical purity. To help the reader appreciate the implications of these issues to structure–odor relationships and to provide background information on the methods available for measuring odor, I have included a second introductory section entitled "Odor Measurement".

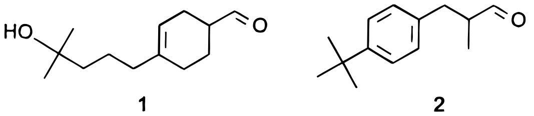
II. The Biochemical Study of Olfaction

Prior to the early 1980s the biochemical study of olfaction had been virtually neglected and thus chemists were forced to postulate mechanisms of olfaction based upon observed correlations between odor and molecular properties. The "stereochemical theory", which was postulated by Amoore[6] in 1952, links odor quality to molecular shape and incorporates the concept of primary odors. The primary odor theory is analogous to the visual perception of color. Amoore considered that all odor sensations are based on various combinations of a limited number of primary odors, with each primary odor being detected by a different receptor in the nose. Seven primary odors were originally suggested on the basis of their frequency of occurrence in the literature: ethereal, camphoraceous, musty, floral, minty, pungent, and putrid.[7] Amoore subsequently carried out "specific anosmia" experiments in an attempt to prove the existence of primary odors and identify them all. This work was inspired by Guillot's[8] suggestions that specific anosmia, the inability to detect one particular odor, was due to the affected person lacking one of the primary odor receptors. One of the main objections to the stereochemical theory is that there are many examples of substances that have a similar shape but very different odors because of a difference in functional group.

The vibrational theory was first postulated by Dyson[9] in 1937 and later extended by Wright[10] in the 1950s and 1960s. They believed that olfactory receptors selectively enter into resonance with odorous molecules. Objections to this theory concern, firstly, optical isomers and, secondly, isotopic substitution. Enantiomers have identical far-infrared spectra whereas in some cases, but not always, their odor qualities can be quite different. Deuteration of an odorant molecule alters the vibrational frequencies of the molecules but does not change its odor. These and other old "theories of olfaction" have been reviewed recently by Laffort.[11] Recently Wright's theory has been given a new lease on life by Turin[12] who has proposed an electron tunneling mechanism as the olfactory detection method. He postulates that electron tunneling through a molecule excites it vibrationally and that therefore there is a degree of correlation between odor and vibrational spectra.

The basic anatomy of the nose and olfactory system has been understood for some time. In mammals, for example, the initial detection of odors takes place at the posterior of the nose, in the small region known as the olfactory epithelium. In the human adult this region appears to be 1–2 cm^2, containing an estimated 6 million olfactory signal cells (neurons) on each side. From the dendrite end of each neuron there are several hairlike appendages called cilia which extend outward into the mucus that covers and protects the olfactory epithelium. The initial events of odor discrimination are thought to involve the interaction of odorous molecules with specific receptors on the cilia. At the other end of the neuron the axon projects directly through the cribriform plate to the olfactory bulb in the brain. In the bulb these axons synapse onto secondary neurons known as mitral cells. This synapse, which is known as a glomerulus, is complicated and consists of a single mitral cell upon which approximately 500 olfactory axons converge; from there signals are relayed to higher regions of the brain. The peripheral location of olfactory neurons, their remarkable capacity for post-natal regeneration and their direct axon link to the brain sets olfactory neurons apart from other neurons of the central nervous system. A detailed account of the anatomy of the human olfactory neuroepithelium is provided by Morrison and Moran.[13]

Recent research into the biochemistry of olfaction was stimulated by the discovery, in the mid-1980s, that the level of cyclic adenosine monophosphate (cAMP) in isolated olfactory cilia increased rapidly when the cilia were exposed to certain odorants. It was subsequently demonstrated that odorants which had no effect on the level of cAMP-induced a rapid change in the levels of inositol triphosphate (IP$_3$). The involvement of these two secondary messengers in other transduction mechanisms, that is the conversion of chemical signals into electrical signals interpretable by the brain, is well known. An increase in the amount of either cAMP or IP$_3$ causes the opening (gating) of ion channels. Influx of positive ions into the cell initiates a decrease in voltage across the cell membrane which ultimately results in the generation of a nerve impulse, or an excitatory response. The role of secondary messengers in olfaction is reviewed by Breer[14] and the diversity of olfactory membrane conductance by Dubin.[15] Dubin's review includes a discussion of three classes of mechanisms that have been proposed to underlie odor transduction. These are (1) direct gating of ion channels by odorants, (2) the alteration of membrane fluidity by odorants and (3) indirect odor transduction through receptor proteins which are linked to secondary-messenger-dependent pathways.



1 2

Figure 1. Fragrance ingredients used in ligand–receptor modeling experiments.

The above findings on the odor-induced cAMP and IP$_3$ responses fit well with the discovery that guanine nucleotide binding proteins (G-proteins) were also involved in olfactory transduction. G-proteins mediate guanosine triphosphate (GTP)-dependent responses which act as intermediaries between ligand receptors and targets such as adenylate cyclase and phospholipase C, the intracellular enzymes responsible for the production of cAMP and IP$_3$ respectively. In other nonolfactory organs the above type of transduction process is linked to receptor proteins that are inserted into the cell membrane and that cross the membrane in seven places. Thus, it was widely postulated that odor receptors might also belong to this seven-helix family of G-protein-coupled receptors. Guided by this idea, Buck and Axel[16] in 1991, set out to find the genes encoding odor receptors. Using the technique of gene cloning they successfully cloned and characterized 18 putative receptor proteins from rat olfactory tissue. Other workers have extended the cloning to mice, humans, dogs, and fish, producing hundreds of candidate molecules that could be olfactory receptor proteins. However, these proteins are still poorly characterized and their binding affinity for odorants has yet to be demonstrated, although there is suggestive evidence that at least one of these receptors can actually respond to odor molecules. Raming *et al.*[17] expressed the rat receptor protein (OR5) into the baculovirus-Sf9 cell which, on stimulation with a mixture of two fragrance ingredients, Lyral (**1**) and Lilial (**2**) (Figure 1), showed a 2-fold increase in the level of IP$_3$. Hypothetical Lyral binding sites on the OR5 receptor have been identified by Singer and Shepherd[18] in simulated docking experiments using molecular modeling. The results point to a potential binding pocket in the OR5 receptor which is made from residues distributed in helices 3 through to 7. This work supports the suggestion by Buck and Axel[16] that helices 3, 4, and 5, which exhibit wide sequence diversity from one receptor to another, are involved in odorant binding (Figure 2). A similar molecular modeling experiment has been carried out by Bajgrowicz and Broger[19] using Lilial as the ligand. The putative binding site obtained from this experiment was formed from eleven amino acids of helices 3, 4, 6, and 7. The two possible binding orientations of Lilial both possessed certain ligand–OR5 receptor interactions which were similar to those identified by Singer and Shepherd for Lyral. Interestingly, both Lyral and Lilial belong to the lily of the valley odor family. However, the modeling of this important class of proteins is highly speculative because of insufficient knowledge of the olfactory mechanisms

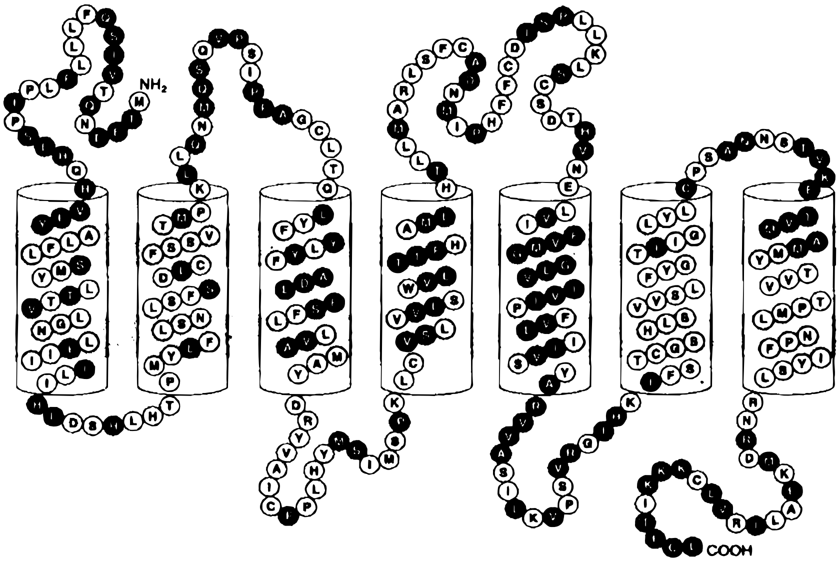


Figure 2. A diagram of one of the putative olfactory receptor proteins showing the positions of sequence diversity. Each ball represents an amino acid; positions shown in white share the same residue in 60% or more of the 10 clones studied, positions shown in black are the more variable residues. The cyclinders represent seven α-helices of the cDNA clone I15 spanning the membrane of the receptor cell with its N-terminus located extracellularly and its C-terminus intracellularly. (Reprinted from ref 16. Copyright 1991 Cell Press.)

and the assumptions which have to be made regarding the tertiary structure of the protein. Thus models of this type will be incorrect in many parts, but nonetheless are very useful in suggesting experiments to further probe structure−activity relationships.

The aforementioned gene-cloning experiments suggest that odor discrimination involves a large number of distinct receptors each capable of associating with a small number of odorants rather than a few odor receptors each capable of interaction with multiple odorant molecules. Currently, the number of receptor types is estimated to be as high as 1000. This raises the question of how are these receptors distributed. Are individual members of this receptor family expressed by every olfactory neuron or by only a small subset of neurons? Evidence to date supports the latter. Each sensory neuron expresses only one receptor and is therefore functionally distinct. The question then emerges as to whether neurons expressing the same receptor are localized in the olfactory epithelium or are randomly distributed, but with their axons converging onto discrete glomeruli. Recent studies[20−23] have shown that the olfactory epithelium is divided into broad zones according to the types of receptors found in each zone, but that within each zone there is a random distribution of neurons expressing the same receptor and that members of each subset send their axons to only one or a few of some 2000 glomeruli.[24] There is, however, evidence that at least one receptor subtype (OR37) is expressed in sensory neurons clustered in very similar positions within the nasal cavity.[25] For an overview of how odor information is encoded, the reader is referred to the articles of Math[26] and Axel.[27]

In contrast to the olfactory receptor proteins, odorant binding has been successfully demonstrated for a particular class of proteins present in the olfactory mucus. These odorant-binding proteins were first discovered at the beginning of the 1980s in the search for olfactory receptors using radioactively labeled 2-isobutyl-3-methoxypyrazine. Initially they were called "pyrazine-binding proteins", but later, when odorants of different chemical classes were also found to be good ligands, the more general name "odorant-binding proteins" (OBPs) was adopted. Their affinity for odorants and pheromones suggests a role in olfactory perception but, although a great deal of information has been accumulated during the last few years on the structures of these proteins, their function is still unknown. One hypothesis suggests that OBPs carry odorant molecules across the aqueous barrier of mucus to and from the membrane receptor proteins. This is based upon the structural similarity of OBPs to a large family of carrier proteins called lipocalins. A second hypothesis is that OBPs play a filtering and buffering role. When a high concentration of odorant enters the nose the OBPs trap most of the molecules that would otherwise inactivate the olfactory receptors for a long period. The recent discovery of more than one type of OBP in the same animal species may suggest new hypotheses, including a role in odor discrimination. The data available to date on odorant-binding proteins has been reviewed recently by Pelosi.[28]

In summary, breakthroughs in the biochemistry of olfaction over the last few years include the identification of proteins and secondary messengers which may play some role in olfaction. Although this has provided useful clues on the possible biochemical mechanism of olfaction, it should be remembered that responses evoked *in vitro* by odorants may not necessarily occur *in vivo* and vice versa. Thus, much remains to be discovered about olfactory transduction. Recent reviews on this topic are provided by Breer *et al.*[29] and Ronnett.[30]

III. Odor Measurement

Aroma chemicals have two sensory odor properties: intensity (strong, moderate, weak) and quality (floral, woody, etc). The first very important step in the determination of a relationship between these properties and molecular structure is the collation of good, precise, reproducible odor data. Without this all subsequent SAR work is a waste of time!

A. Physical Methods

Both odor intensity and quality are very difficult to measure objectively with physical instruments. Olfactometers[31] simply generate and deliver an odorous air sample of known concentration to a human subject for assessment. Development of an instrument which could also analyze odors has been an area of active research since the 1950s. Progress in this area is reviewed in an excellent article devoted to the measurement of odors by Neuner-Jehle and Etzweiler.[32] (The reader is also referred to this article for more detailed information on the other aspects of odor measurement which have only been briefly mentioned in this section.) Today sophisticated "electronic noses" are available which are, for example, capable of identifying the aroma from different brands of coffee and of monitoring the fragrance emitted from a bar of soap over a given period of time.[33] These modern electronic noses generally consist of an array of gas-sensitive semiconductors which are connected to a neural network. The signals recorded by the sensors produce a characteristic pattern for a given odor. Once the neural network has been trained using a set of known samples, it can be used to assess test samples against the standards of the training set. Fast analysis time and good discriminating power make these "artificial noses" very useful quality control tools. However, they are still a long way from being able to report odor data suitable for structure−activity work, since the properties of odorants which are responsible for determining the odor character and odor intensity perceived by man are still unknown and thus cannot yet be incorporated into the design of new artificial gas sensors. This is exemplified by the recent work of Wünsche *et al.*[34] They compared the odor intensity results from a human panel with those obtained using an electronic nose. In all cases, the human nose was more sensitive than its electronic counterpart. The response to concentration changes was also different for the two "noses". The electronic nose was shown to respond linearly, whereas the human nose responds logarithmically.

B. Physiological Methods

Measurable physiological responses to odor stimuli include changes of electrical potential at the olfactory bulb or olfactory receptor. Attempts have been made to correlate such electrical activity to odor perception. Although successful odor quality relationships still remain elusive, it has been shown that the intensity, or more correctly the concentration, of an odorant stimulus is related to the amplitude of a DC-recorded electrical potential and to the frequencies of an AC-recorded electrical impulse. Since these techniques rely on the use of implanted electrodes there have been only a few studies using human subjects.[35−38] The majority of publications describe the measurement of electro-olfactograms in animals such as frogs, fish, rodents, rabbits, and salamanders.[39,40] The relevance of such findings in animals to human olfaction remains questionable.

Electrical activity in the brain is one electrophysical response which can readily be used with human subjects since it is a nonintrusive, simple, and painless technique. Small disk-shaped electrodes are affixed to multiple locations on the subject's scalp using conductive gel and then, during presentation of an odor, the changes in cortical electrical activity are recorded using electroencephalogram (EEG) techniques. These have been used to study the unpleasantness and pleasantness of odors, the arousal and sedative effects of different odors and odor intensity. A recent review on EEG response to odor stimuli is provided by Behan and Richardson.[41] Often the EEG data is displayed as averaged scalp topographical maps. Great care must be taken in the interpretation of such maps because of the spatial smearing associated with EEG measurement. The cause of this smearing is the relatively large distance and the interceded brain tissues between the source of brain electrical activity and the recording site (the scalp). Measurement of magnetic fields enables locations of brain activity to be more accurately identified since magnetic fields are less distorted by brain tissues than electrical fields.[42−44] However, one of the biggest problems with measuring odor-evoked brain activity is the separation of this data from brain activity associated with nonolfactory stimuli (e.g. the process of sniffing, the anticipation of an odor) or odor-induced cognitive processes (e.g. thoughts of eating, memories of a particular restaurant). In addition, although the time delay between presentation of an odor stimulus and the measurement of brain activity can be as low as 50 ms, it may still be too long to tell us anything about the first stages of odor transduction (i.e. the triggering of receptors). The area of human EEG and odor response has been reviewed by Lorig.[45]

C. Sensory Methods

1. Reproducibility

It is clear from the above paragraphs that in the absence of an objective method of measuring odors, the only way to obtain a human's perceptual response to an odor is to ask him for a verbal expression of the odor intensity and quality. However, odor classification of this type, which is based on sensory associations, could be misleading since it might not be directly correlated with the receptor mechanism. In addition recognizing and describing an odor in words is no easy task. Cain[46] found that, in a study of common household odors, subjects could name only approximately 50%. Also the odor of one substance may by described in different words by different people. The problems associated with subjectivity and fragrance vocabulary are minimized by the use of an expert panel and a standard glossary of odor descriptors. Although most perfumery institutes have their own fragrance dictionary, which can contain, for example, as little as 42 odor descriptors[47] or, more commonly, something in the order of 150,[48] there is no universally accepted standard list. The

3

Figure 3. Odor properties of (*R*)- and (*S*)-carvone.

International Standard for the initiation and training of assessors in the detection and recognition of odors[49] provides a list of only 24 odoriferous substances which serve as references for several groups of odors. Panelists should not be anosmic (unable to smell) or have specific hyposmia (reduced sensitivity) or hyperosmia (increased sensitivity) to the odors under consideration.

The absence of a universal odor language and the subjective nature of odor perception are just two factors which contribute toward discrepancies in odor descriptions from different sources. Other factors include different methods of sensory assessment and the presence of trace impurities resulting from either different sources of starting materials, methods of preparation, or methods of purification. Even the smallest trace of a strongly odoriferous material can alter the odor profile of a sample completely. This dilemma is nicely illustrated by Weyerstahl[5] in his review on “Odor and Structure”. He compares his own odor evaluations for a series of unsaturated aldehydes with those of Belitz and describes (using the preparation of sesquicineole as an example) how the use of reagents such as $[(Ph_3P)_2Cu]BH_4$ can lead to the presence of very unpleasant phosphine notes even though the product appears pure by gas chromatography. Sulfur-containing reagents present a similar problem. The implication for structure–odor relationship work is that literature odor descriptors cannot necessarily be regarded as a reliable source of odor data. One particular structure–odor relationship worthy of mention is the effect of chirality on odor. In the majority of cases, the reported odor differences for enantiomers are so small that they have often been explained away as due to the presence of trace impurities. The most striking differences tend to occur in rigid molecules such as carvone (**3**) (Figure 3). For this compound at least it has been shown, by enantiomeric interconversion, that the qualitative odor differences are real and not due to traces of odorous byproducts.[50] For further reading on the sensory properties of optical isomers the reader is referred to the recent reviews of Boelens,[51] Chastrette,[52] Koppenhoefer,[53] and Mosandl.[54,55]

2. Classification of Odors

Semantic descriptors are important in structure–odor relationship (SOR) work for identifying groups of compounds with similar odors. Compounds which have an odor that can be described using only one or two descriptors are relatively easy to classify. This is one reason why SOR studies have been centered around distinct odor groups such as ambergris, bitter almond, musk, and sandalwood. A second reason is that the structures of the compounds associated with these well-defined odor groups tend to be fairly rigid and thus easier to model than the more flexible molecules, which tend to have more complex odor profiles. Flexible molecules can potentially adopt a much larger number of energetically favorable conformations, each of which may be responsible for triggering a different odor response. Yoshii *et al.*[56] investigated the stable conformations of (*R*)-ethyl citronellyl oxalate and found that the most stable compact conformations fitted their previously published benzenoid musk model[57] and that one of the stable conformations partially resembled one conformer of (*S*)-citronellol, a rose odorant. They concluded that these conformations could be responsible for ethyl citronellyl oxalate’s main odor quality (musk) and its secondary odor quality (rose) and that other notes, such as woody and fresh, might be explained by further conformational comparisons with other structure–odor models.

Semantic descriptors have been used in the development of numerous schemes for the classification of odors. Early work in this area is reviewed by Harper, Bate Smith, and Land in a book dedicated to odor description and classification.[58] The common scheme employed for the broad grouping of odors is based on associations with natural products. Thus materials which smell of rose, lily of the valley, and jasmine are all placed in the floral family. However, from an SOR point of view there is no logical reason why specific odor characters should be grouped in this way. Boelens in 1981 studied over 300 aroma chemicals using 30 different odor descriptors.[59] This afforded 14 groups of compounds having very similar odor aspect patterns within each cluster. More recently, Abe[60] used a set of 126 descriptors to characterize an impressive 1573 organic compounds. Cluster analysis showed there to be 19 categories of odor–categories which were reported to agree with early proposals for the classification of primary odors.

An alternative way of measuring odor, which not only avoids some of the problems associated with the use of a fragrance vocabulary but which also leads to quantified odor quality data, is the measurement of odor similarities.[61] Materials are rated against reference standards and given, for example, a score of 0–100%, where 0% corresponds to an odor which is completely different from that of the standard and 100% to an odor which is identical to that of the standard. It is assumed that if two odorants cannot be clearly discriminated from each other they must, on the whole, be interacting with the same peripheral receptors and share common quality determining parameters. Nevertheless, this approach still has weaknesses: for instance, two odorants may be 98% similar but still easily discriminated. Using odor similarity measurements, molecules can be arranged spatially to form a map in which compounds having similar odors are represented by a cluster of points while those which are different are far apart. After the maps are obtained, they can be interpreted by a wide range of statistical techniques to determine those aspects of the molecule which are responsible for their odor qualities. This technique was used by Schiffman to study the correlations between 25 physiochemical parameters and the odor qualities of 39 odorants.[62] These materials covered a wide range of odor characteristics. Among the parameters used were molecular size, molecular weight, the number of double bonds, functional groups, solubility, and raman spectral lines.

In addition to odor classification, measured odor similarities can be used as the dependent variable in the development of a quantitative SAR equation. Odor intensity values are also often used for this purpose. The advantage of a quantitative model over a classification model is that it can be used, for example, to predict how fruity a compound is likely to be rather than just whether or not it is likely to have fruity character. Odor similarities obtained by Amoore have been used by both himself and other SOR workers in the study of bitter almond,[63−65] floral,[64] and ethereal[64] odorants. Boelens, another practitioner of odor similarity measurements, has used them to develop equations relating bitter almond,[66] fruit,[67] jasmine, and lily of the valley odor qualities to a range of structural and physiochemical parameters of the corresponding groups of compounds.

3. *Gas Chromatography Olfactometry*

A useful technique for checking the olfactory purity of a sample is gas chromatography olfactometry (GCO), more commonly referred to as GC sniffing. Provided that the GC conditions adequately separate the components of a mixture, each component can be smelt in an olfactorily pure state at the exit port of a GC column. It is not uncommon for an odor to be perceived at a position in the gas chromatogram where there is no peak. This illustrates the vastly superior sensitivity of the human nose over, even today's, most sensitive GC instruments. Repeated analysis of the same sample at successively higher dilutions is a methodology commonly used to identify the components which make the greatest contribution to the overall odor of that sample. An area in which this technique has found wide applicability is the analysis of complex natural products. Examples of its use in the identification of a new fragrance chemical and in the determination of the relative odor strength of two enantiomers are provided in the aforementioned article of Neuner-Jehle and Etzweiler.[32] GCO dilution analyses, such as CHARM analysis[68] and Aroma Extract Dilution Analysis (AEDA),[69] can also be used to determine the odor threshold value of an odorant. The odor threshold value is, in theory, the minimum concentration of a compound detected by the human nose. Its determination is based on a statistical concept: it is the concentration at which a subject (or group of subjects) gives a positive response in 50% of the trials. These values can be calculated from the concentration and injection volume of the solution and the GC split ratio. Threshold data can also be obtained from an olfactometer by successively reducing the concentration of odorant in the air stream. Odor threshold values which have been measured under identical experimental conditions can be used to give an indication of the relative potency of fragrance ingredients. For example, Cometto-Muñiz and Cain[70,71] have found that the detection threshold values in ppm for 2-phenylethanol (which has a rose-like odor), *tert*-butyl acetate (camphoraceous), and toluene were 1.3 million, 9.1 thousand, and 76 times lower, respectively, than that of acetone.

Gas chromatography olfactometry (GCO) is time-consuming compared to the smelling of a sample from a smelling strip or at the outlet of a conventional olfactometer. This limits the number of analyses that can be repeated for the same sample at the same concentration, which in turn raises the issue of reproducibility and subjectivity. Other drawbacks are that the technique does not allow the simultaneous comparison of different samples and that it is unsuitable for heat-sensitive materials. Advantages include the ability to analyze minute quantities of a sample and to organoleptically assess pure components. A brief overview of recent developments in gas chromatography olfactometry is provided by Boelens *et al.*[72]

4. *Odor Intensity*

The determination of odor threshold concentrations using either GC sniffing or an olfactometer is just one way of quantifying the odor intensity of a compound. Two alternative ways of measuring the relative odor strengths of different odorants are (1) the concentration of a compound required to produce a perceived odor intensity equivalent to that of 1-butanol at a given concentration (usually 87 ppm) and (2) odor intensity ratings, which can either be a numerical scale or simply a division into very strong, strong, moderate, weak or odorless.

For further reading on the measurement of odor intensity the reader is referred to the articles of Köster[73] and Neuner-Jehle *et al.*[32]

When quantifying odor intensity it is very important to be aware of Stevens' law.[74] This relates the perceived intensity (I) of an odorant to its concentration (C) in log/log co-ordinates (Figure 4). The increase in perceived odor intensity with concentration is represented by a straight line. The slope indicates how fast odor intensity rises with concentration and the intercept defines the threshold concentration where odor intensity changes from not perceived to just being perceived. The fact that the

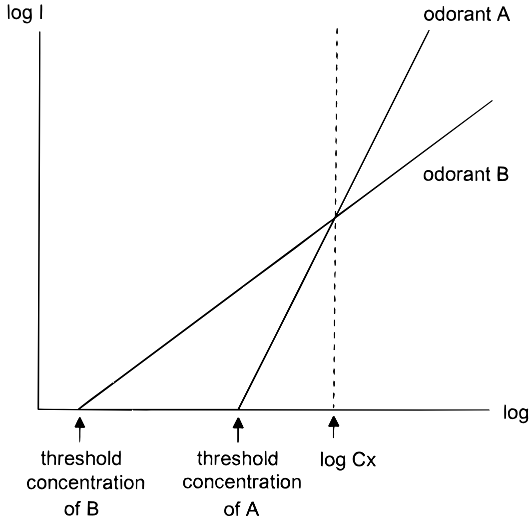


Figure 4. Diagram showing the effect of the concentration on the relative perceived intensities of two materials, A and B, which have different log I/log C gradients.

slope varies from one odorant to another causes problems when comparing the odor intensity of a range of compounds. For example, in the case of A and B in Figure 4, it would be concluded from the odor threshold concentrations that B is stronger than A. However, above a concentration of C_x the reverse is true and A is perceived as being more intense than B. The concentration of an odorant can also affect its odor characteristics. The classic examples are thiols, which at high concentrations exhibit unpleasant sulfurous odors but which at very low concentrations can have very pleasant grapefruit, pineapple, or passionfruit notes. For example, *p*-menth-1-ene-8-thiol, which is one of the most potent odorants known, has a characteristic grapefruit note at the ppb level or below, whereas concentrated samples smell extremely powerful and nauseous.[75]

Because both the relative perceived intensities of a series of compounds and the odor characteristics of a single compound can vary with concentration, it is very difficult to decide which of the above odor-intensity quantification techniques should be used for SAR work. In addition, just as the reported odor characteristics of a compound can vary from one published source to another, so can odor threshold data. For example, published detection odor threshold values in air for chloroform vary from 30 to 3000 mg/m^3 air and those for 4-hydroxy-3-methoxybenzaldehyde (vanillin) from 5×10^{-3} to 1×10^{-6} mg/m^3 air.[76]

Christoph and Drawert[77] used threshold values obtained from GCO dilution analysis to study the relationship between structure and odor intensity for a series of homologous saturated aliphatic aldehydes, alcohols, acetates and ethyl esters, and monoterpene hydrocarbons and alcohols. They found that the compounds with the lowest thresholds are molecules with 8, 9, and 10 heavy atoms in the straight chain. The thresholds of acyclic monoterpenes were shown to be significantly lower than those of monocyclic terpenes and these in turn still lower than those of bicyclic compounds. An additional prerequisite for a low threshold appeared to be branching of alkyl chains.

Branching was also considered to be associated with odor strength by Jurs and Edwards[78] in their study of 58 structurally diverse compounds. This group of workers quantified odor intensity by determining the concentration (*C*) of these compounds required to produce an odor strength equivalent to that of 1-butanol at 87 ppm. The following molecular criteria were also considered to be important in determining odor intensity: (1) In the molecular weight range of their data set (41−168), increasing molecular weight led to a lower value of log (*C*). (2) Odor intensity increased as the partial charge on the most negative atom became more negative. (3) Unsaturation in a molecule led to an increase in odor strength.

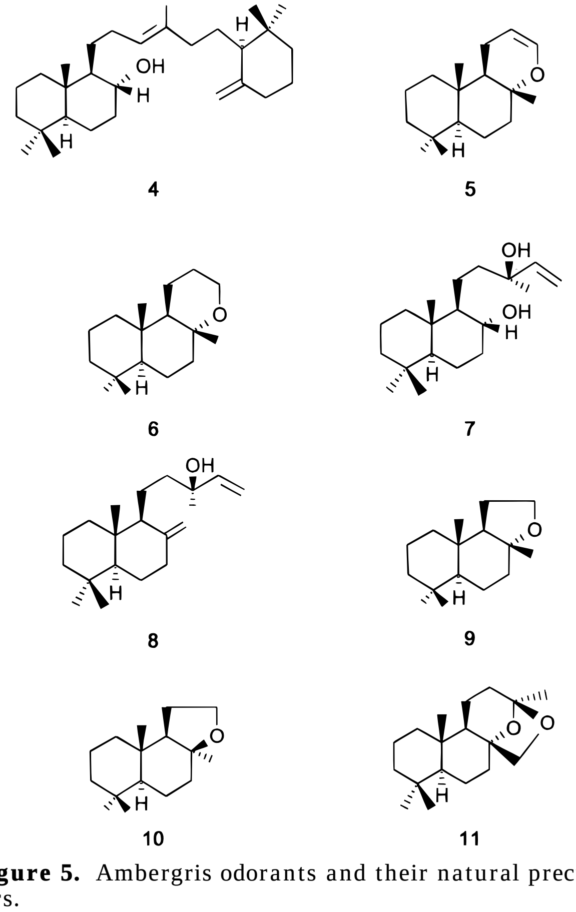
Jurs, in addition to looking at the overall odor intensity, also focused on the strength of one individual character, sweetness of odor.[79] No direct structure−sweetness relationship could be uncovered using his diverse set of 73 industrially important fragrance compounds. A logarithmic transformation of the sweetness did provide substantially improved statistics. The difficulties encountered in this study prompted Jurs to criticize the procedures used to obtain the data: 120−150 panelists characterized the odor profiles of the fragrances using a glossary of 146 standard semantic descriptors. The model's limited applicability may also be a function of the immense structural diversity represented in the data set. By restricting his studies to a homologous series and by using odor threshold data from a single source, Jurs[80] successfully developed QSARs for a set of 53 alcohols and a set of 74 mono- and disubstituted pyrazines. However, many published SORs rely on data from mixed sources and this must be borne in mind when considering their results.

IV. QSAR Studies in Specific Odor Areas

A. Ambergris

Ambergris is one of the few natural fragrance materials of animal origin. It is secreted in the stomach or intestinal tract of the sperm whale and released into the sea in the form of a gray to black stonelike mass. When exposed to sunlight, air, and sea water, the material gradually fades to a light gray or creamy yellow color. At the same time the main component, the triterpene alcohol ambrein (**4**, Figure 5), is oxidatively degraded. Some of the products resulting from this chemical process are responsible for the organoleptic properties of ambergris; among the first to be identified were the tricyclic ether (**5**) and its hydrogenated analogue **6**.[81,82]

Other natural raw materials from which ambergris substances can be synthesized are sclareol (**7**) ob-



4 5 6 7 8 9 10 11

Figure 5. Ambergris odorants and their natural precursors.

trans-decalin system - a requirement for ambergris odor

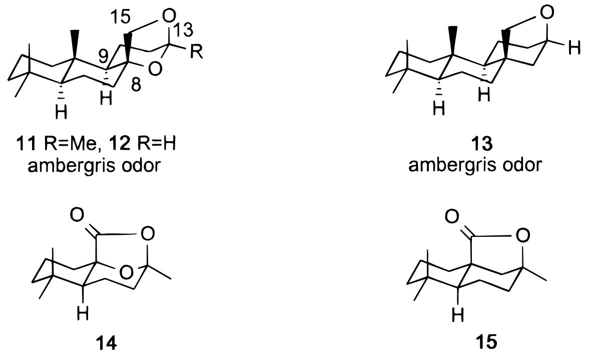
cis-decalins tend to be inactive

Figure 6. Ohloff's "Triaxial Rule".

tained from clary sage (*Salvia sclarea*), and manool (**8**), obtained from Pink Pine (*Halocarpus biformis*, formerly *Dacridium biforme*). Sclareol can be transformed into the tricyclic ethers **9** and **10**.[83] Compound **9** is known by various trade names such as Ambrox (Firmenich), Ambroxan (Henkel) and Amberlyn (Quest). It has been a key ambergris-type ingredient in perfumery for along time although it was only in 1977 that it was first reported as being among the odoriferous constituents of ambergris itself.[84] Manool can be degraded to the tetracyclic ketal **11** (Jeger's ketal), which also has an intense amber note. For further details on the occurrence, properties, and odoriferous constituents of ambergris itself and of the ambergris odorants derived from other natural sources the reader is referred to the review articles of Ohloff[85] and Cambie.[86]

All of the aforementioned ambergris fragrances are derived from natural starting materials, some of which have become increasingly difficult to obtain. This, along with the growing demand for ambergris odorants, stimulated the search for more accessible and cheaper substitutes. This included the preparation of a large number of tricyclic 5- and 6-membered ring ethers, which on careful examination led to Ohloff's well-known structure–activity relationship: the "triaxial rule of odor sensation".[87] Ohloff postulated that in order for a material to possess an ambergris odor, it must have a molecular structure containing a decalin ring system with three axial groups. These groups should be located 1, 2, and 4 relative to each other, and one of them must be an oxygen function (alcohol, ether, or ester) (Figure 6). The substituents in the 1- and 2-positions can be hydrogen, since their main function is to ensure a *trans* configuration of the decalin system. *Cis*-linked derivatives tend to be either odorless or to have odor qualities which are quite distinct from that of ambergris; often a camphor-like odor predominates.

For the intramolecular C_{18} acetals **11** and **12** it has been suggested that the triaxial substituents are the 9α-proton, the C-15 methylene group, and the C-13 oxygen atom and that the function of the C-8 oxygen is to simulate part of the decalin ring system (Figure 7).[87–89] Indeed, replacement of the C-8 oxygen functionality by a methylene group yields a cyclic ether **13** which still retains a sweet ambergris odor of moderate intensity.[90] This phenomenon, however, is not universal: the oxalactone **14** has a strong amber odor, whereas its carbon analogue **15** is odorless. Ohloff's reasoning is that differences in the dielectric polarizations of these two compounds will affect the orientation of these molecules as they approach the receptor membrane. Thus the oxalactone approaches the receptor in the correct orientation for interaction whereas the carbon analogue does not.



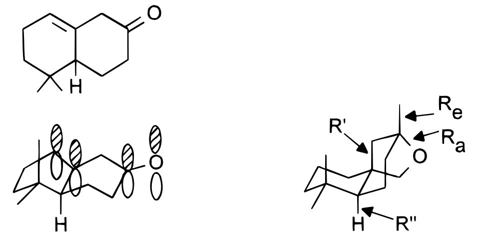
11 R=Me, **12** R=H
ambergris odor

13
ambergris odor

14
ambergris odor

15
odorless

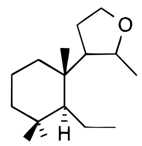
Figure 7. The relative role of the oxygen atoms in intramolecular acetals according to the "Triaxial Rule".



16

17

Figure 8. Electronic factors and the "Triaxial Rule".



18

Figure 9. Vlad's cyclohexyltetrahydrofuran.

Examples of ambergris odorants which do not obey Ohloff's original "Triaxial Rules" include the β-γ-unsaturated ketone **16** and the *cis*-decalin compound **17** (Figure 8). Ohloff's explanations are that in compound **16** the π-orbitals of the double bond and the carbonyl group fulfill the role of two of the axial substituents and that in compound **17** the function of R_a and R_e is to position the ether oxygen such that its lone-pair orbitals are perpendicular to the bonds of R′ and R″. These explanations really do seem to be stretching the rules to make the results fit.

Winter has focused on one particular structural aspect of ambergris odorants, namely the steric accessibility of the functional group. The assumption is that this property provides an estimate of the degree of possible interaction between the O atom and a hypothetical H-bond donor group (OH) on the receptor. Winter found that when the accessible surface area was less than 6 $Å^2$, compounds were inactive.[91,92] Winter subsequently used this parameter to correctly predict the ambergris activity of five novel Amberlyn analogues.[93]

In 1983 Vlad and co-workers discovered a new type of ambergris odorant, the cyclohexyltetrahydrofuran **18** (Figure 9).[94] The absence of a decalin ring system in this compound presumably inspired Vlad's group to look for an alternative structure–ambergris odor relationship.[95,96] They started with a set of 94 compounds which they divided into two classification groups: active and inactive. The active group con-

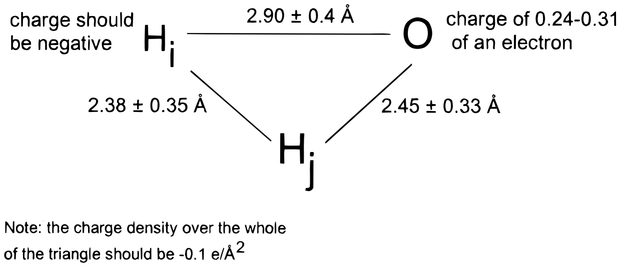


Figure 10. Vlad's ambergris triangle.

tained 59 strong-smelling ambergris compounds and included some examples which clearly did not fulfill Ohloff's triaxial rule. They concluded that structural and stereochemical features, such as bond angles, bond lengths, and distances between specific atomic groups, are not enough to explain the origin of the observed ambergris odor properties. They suggested that electronic properties, such as the atomic contribution to the highest occupied molecular orbital (HOMO) or lowest unoccupied molecular orbital (LUMO), should also be considered. This approach which combines the use of electronic structure and molecular conformation (topology) is known as the electron-topological (ET) method. When the ET method was first applied to the study of ambergris odorants, Vlad and his co-workers studied the electronic structure of only 10 representatives from their original data set of 94 (6 active, 4 inactive). The electronic properties were calculated using the CNDO/2 method with structural parameters taken from X-ray analysis data. They concluded that in the active compounds there is a LUMO (or a nearby unoccupied MO) with a large contribution from the atomic orbital of two hydrogen atoms which spatially form a triangle with an oxygen atom. The dimensions and charge distribution of this so-called "Ambergris triangle" are shown in Figure 10. The negative charge on the hydrogen atom furthest away from the oxygen atom is somewhat surprising. However Vlad does comment that "this statement is not very strong in view of the approximations used in the calculations".

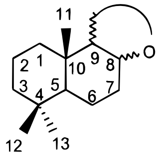
In a more recent electron-topological investigation, the electronic and steric characteristics of 163 compounds (82 active, 81 inactive) were described in terms of electronic-topological matrices of contiguity (ETMCs).[97,98] In this approach each compound is represented by an n^2 quadratic matrix, n being the number of atoms. Since this square matrix is symmetric with respect to the diagonal elements, only the upper half is usually shown (Figure 11). The diagonal elements are represented by electronic atomic properties such as atomic charge, HOMO or LUMO energies, polarizabilities, and so on. The nondiagonal elements are of two kinds. If the atoms on the two edges of the matrix are chemically bonded the nondiagonal elements are represented by electronic properties of that bond and can be, for example, bond orders, Wiberg indices or bond energy. If the two atoms are not chemically bonded the nondiagonal element represents the interatomic distance. A more detailed account of the principles of the electron-topological approach may be found in the literature.[99] In the ambergris study the electronic properties used for the atoms and bonds were the

ETMC for fragment I

O	C_1	C_4	C_5	C_6	
-0.29 to -0.23	4.40-5.90	5.15-6.65	4.15-5.65	3.35-4.85	O
	0.01-0.07	2.77-3.27	2.30-2.80	3.68-4.18	C_1
		0.02-0.08	**0.72-1.22**	2.35-2.85	C_4
			0.01-0.07	**0.76-1.26**	C_5
				-0.02 to 0.04	C_6

ETMC for fragment II

C_{11}	C_{12}	
-0.02 to 0.04	3.20-3.70	C_{11}
	-0.01 to.0.05	C_{12}



19

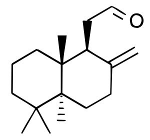
Key to ETMC tables	
0.00-0.00	Wiberg's indices
0.00-0.00	interatomic distance
0.00 to 0.00	effective atomic charge

Figure 11. ETMCs for fragments I and II.

effective atomic charge and the Wiberg index, respectively. By comparing the ETMCs, Dimoglo *et al.* found that each active compound shared two common molecular fragments. Fragment I contained an oxygen atom and four carbon atoms. The distances between these carbon atoms and the oxygen atom were approximately 4.10, 4.90, 5.15, and 5.90 Å. Fragment II contained two methyl groups which were separated by a distance of 3.2−3.7 Å. Both of these methyl groups were attached to quaternary carbon atoms and had the same stereochemical orientation. The ETMCs for these fragments are shown in Figure 11 using the bicyclic skeleton **19**, which is present in the majority of the test compounds, as an example.

An additional prerequisite for ambergris odor was considered to be an oxygen steric accessibility of more than 6 Å^2, a value which corresponds exactly to that quoted by Winter.[91−93] For compounds containing more than one oxygen atom it was shown that the oxygen atom with the highest steric accessibility surface is the one which is involved in activity fragment I. In the case of Jeger's ketal (compound 11, Figure 7) activity fragment I is made up using the C-13 oxygen atom. This oxygen atom has a steric accessibility of 9.59 Å^2. The alternative C-8 oxygen atom has a much lower steric accessibility value of 2.48 Å^2. These findings are in agreement with those of Ohloff,[87] Dey,[88] and Brun[89] who also suggested, on the basis of the triaxial rules, that the C13 oxygen atom was the oxygen atom responsible for the ambergris odor of this ketal. Schvets[97,98] also suggested that if two oxygen atoms in the same molecule both have steric accessibilities of more than 6 Å^2, they would compete for interaction with the receptor and, as a result, destroy the realization of fragment I and deactivate the compound.

In both of the aforementioned electron-topological studies, each compound was analyzed in a single conformational arrangement. This arrangement was determined either from X-ray analysis or by geometry optimization using semiempirical molecular orbital



20

Figure 12. An example of a compound with some degree of conformational flexibility. Only one of the possible conformers was used in the ETMC studies compared with 21 in the CATALYST model of Bajgrowicz and Broger.

calculations. However, the conformation of a molecule responsible for triggering an odor response does not necessarily have to correspond to any of the theoretical minimum energy conformations. Burgen[100] suggests 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 subsite on the receptor. The half-life of dissociation at this subsite is long enough to allow a conformational rearrangement of the drug molecule favoring further binding at subsites. Protein receptors can also change their shape to accommodate incoming compounds. This means that the geometry of the receptor binding sites may not be identical for different compounds even in the same congeneric group. For flexible molecules this creates a huge molecular modeling dilemma—namely the identification of the active conformation upon which to base conformational comparisons and molecular modeling calculations.

The ambergris decalin-type compounds studied by Vlad and Schvets are fairly rigid molecules and thus the number of energetically allowed conformations is relatively low. Exceptions to this include the ring-opened analogues of Amberlyn and other decalin compounds bearing a flexible substituent. For example, the unsaturated aldehyde **20** (Figure 12), which was one of the ambergris odorants in both of the ETMC data sets, was represented by 21 conformations in the recent three-dimensional QSAR study of Bajgrowicz and Broger.[19] These authors used a molecular modeling program called CATALYST in their search for an ambergris osmophore (i.e. the structural elements responsible for the ambergris odor sensation). CATALYST is designed to automatically generate possible biophores (in this case ambergris osmophores) by searching a broad range of energetically allowed conformations while at the same time taking into account the conformational flexibility of the molecule and the possible gain in energy necessary to enter a hypothetical receptor binding pocket. The data set consisted of 62 active ambergris odorants, which had been rated as medium, strong, and very strong, and 82 closely related, but inactive, compounds. Conformational analysis was performed on all compounds but only the 23 most representative and unequivocally rated ones used as the training set in the generation of possible osmophores. These osmophores were then tested using the remaining 121 compounds. 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

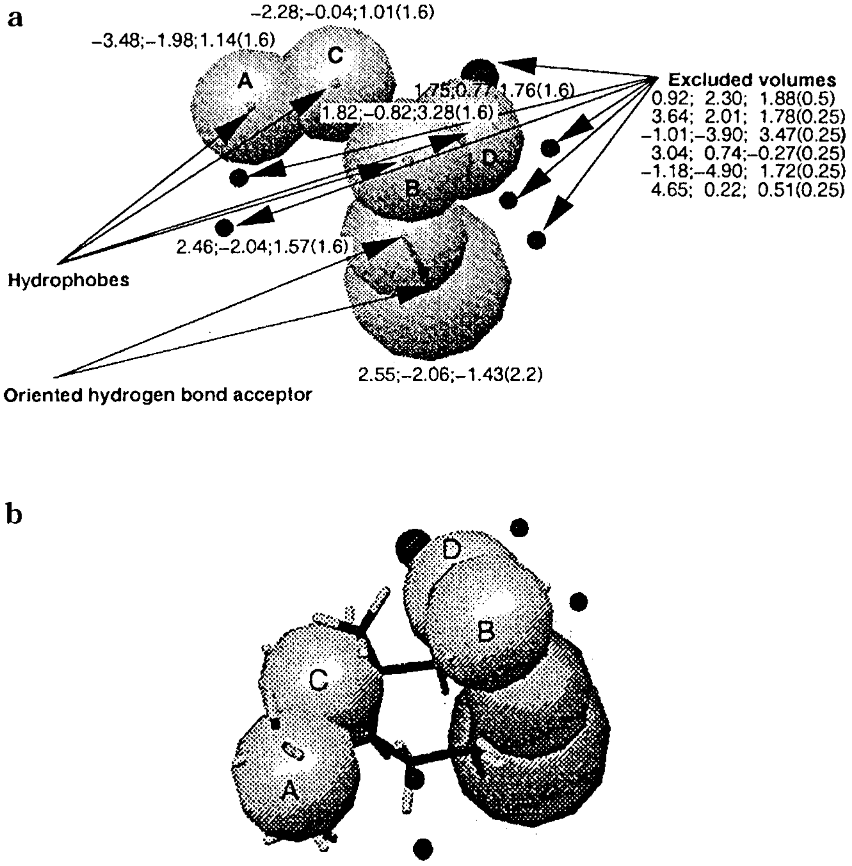
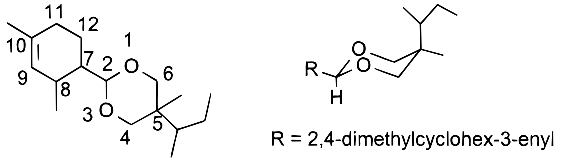


Figure 13. (a) The amber osmophore of Bajgrowicz and Broger. Each feature is characterized by its coordinates and (in brackets) the sphere diameter in angstroms. (b) Amberlyn (**9**) mapped to the five features and the six excluded volumes. (Reprinted from ref 19. Copyright 1995 Anadolu University Press.)



21 **22**

Figure 14. Karanal.

excluded volumes (Figure 13). It is claimed that this osmophore has been successfully used in the design of structurally novel ambergris odorants and that the structure of these will be published after the corresponding patent has been filed.

In 1987, Quest International discovered a new series of ambergris odorants belonging to the 2-cyclohexenyl-1,3-dioxane family.[101] The most notable of these is a very successful aroma chemical registered under the tradename of Karanal (**21**, Figure 14). From the synthesis and organoleptic evaluation of a large number of analogues it was concluded that the general requirements for a material in this family to possess an ambergris odor are as follows:[102] (1) 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). (2) The cyclohexane ring should preferably have a double bond in the 9,10 position, although this is not essential. (3) The cyclohexane ring should carry 1 to 3 methyl groups, preferably 2. However, location of these seems to be more important than number.

The structural requirements are further complicated by stereochemical considerations. For example, Karanal is a mixture of eight pairs of enantiomers of which only four are organoleptically active (three of strong intensity and one of weak). NMR spectroscopy[103] in conjunction with X-ray crystallography[104] has revealed that the active stereoisomers have a *cis* configuration about the dioxane ring with the cyclohexenyl substituent equatorial and the *sec*-butyl group axial **22** (Figure 14).

B. Bitter Almond

For more than 40 years the bitter almond odor of compounds has been a model "*par excellence*" for studying SAR because it is an odor facet which is well-defined. The classical molecules having this smell are hydrocyanic acid (HCN) and benzaldehyde. Both of these materials are produced by the hydrolysis of amygdaline, which is one of the constituents of bitter almonds.[105] Thus the Oil of Bitter Almond, obtained after hydrolysis and steam distillation, is a mixture of predominantly benzaldehyde, but also 2−4% of hydrocyanic acid. Since hydrocyanic acid is water soluble the majority of HCN will be dissolved in the distillation waters and any HCN vapor which has not been condensed is usually vented to the air. Because of its toxicity the 2−4% of hydrocyanic acid is removed from the oil by conversion into insoluble calcium ferrocyanide.

The aldehyde group in benzaldehyde can be replaced by other electron attracting groups of similar size and charge distribution such as NO_2, CN, and N_3 with little variation in the original odor. The valence electron charge distribution for benzenes substituted with these groups was calculated by Lindner and Märtensson.[106] In all cases they found that the end atom of the functional group has a net small negative charge and that the part of the molecule of interest has a similar outer contour.

The odor similarity of benzaldehyde and nitrobenzene is even retained in their alkylated derivatives. The olfactory properties of the methyl, ethyl, isopropyl, and *tert*-butyl analogues were studied by Klouwen and Ruys in 1963.[107] They found that for the *para* and *meta* series the odor quality of both the substituted benzaldehydes and nitrobenzenes changed from almond to cumin as the size of the alkyl substituent increased. In contrast, the olfactory characteristics of the *ortho* compounds tended to approximate to those of the corresponding hydrocarbon.

The odor similarity (OS) of these disubstituted benzenes was rated against benzaldehyde by Amoore[63] in 1971. He showed that the more closely a compound resembled benzaldehyde in terms of molecular shape, the more similar it is to benzaldehyde in odor. These odor similarity ratings were also used by Kier[64] to examine this class of odorants using a structural analysis known as molecular connectivity. The concept of molecular connectivity was introduced by Randic[108] and further elaborated by Kier[109] and involves the calculation of numerical indices which describe the topology of a molecule. The two indices in Kier's bitter almond equation (eq 1) reflect the overall size and branching of a molecule:

$$\mathrm{OS} = 15.02 - 2.122\,{}^{0}\chi^{\mathrm{v}} + 2.424\,{}^{3}\chi^{\mathrm{v}}_{\mathrm{c}} \qquad (1)$$

$$n = 24 \qquad r^2 = 0.878 \qquad s = 0.600$$

where ${}^{0}\chi^{\mathrm{v}}$ is zero-order valence molecular connectivity and ${}^{3}\chi^{\mathrm{v}}_{\mathrm{c}}$ is third-order valence cluster molecular connectivity.

Dearden[65] reexamined Amoore's data in 1994 using a total of 38 parameters. They included log *P*, molar refractivity, heat of formation, energies of the highest occupied and lowest unoccupied molecular orbitals, dipole moment, molecular connectivities and κ indices (a shape index obtained from molecular graphs[110]). He also found that the equation which best accounted for the observed benzaldehyde-likeness contained two molecular connectivity terms, both of which were related to the shape of the molecule (eq 2).

$$\mathrm{OS} = 13.6 - 8.08\,{}^{3}\chi^{\mathrm{v}} + 2.19\,{}^{4}\chi^{\mathrm{v}}_{\mathrm{pc}} \qquad (2)$$

$$n = 26 \qquad r^2 = 0.926 \qquad s = 0.545$$

where ${}^{3}\chi^{\mathrm{v}}$ is third-order valence molecular connectivity and ${}^{4}\chi^{\mathrm{v}}_{\mathrm{pc}}$ is fourth-order valence path cluster molecular connectivity.

Interestingly, all three QSAR's derived from Amoore's data set underpredicted the benzaldehyde-likeness of 3-methylnitrobenzene. This compound was also incorrectly predicted to be a non-bitter almond odorant using the classification model of Zakarya.[111] This model was derived from a set of 40 structurally diverse organic compounds, including benzene, pyrrole, thiophene, acyclic, and cyclic com-

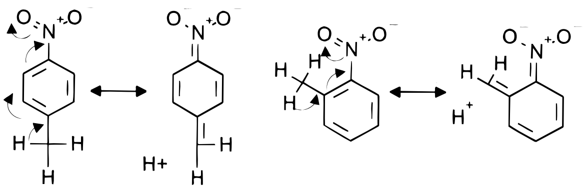
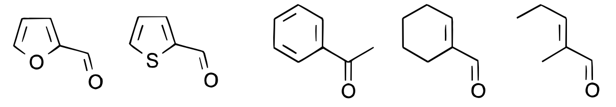


Figure 15. Hyperconjugation effect of ortho and para substituents on the electronic properties of the nitro group.

pounds. The odor of these materials was described with a binary variable (1 for bitter almond smelling and −1 for non-bitter almond smelling). Each molecule was described by 24 molecular descriptors, each a component of an autocorrelation vector. These vectors accounted for the shape, size, and electronegativity of the molecule. The data was analyzed using principal component analysis followed by a linear discriminant analysis. The resulting model was predominantly madeup of components related to the volume and surface properties of the molecules. The model correctly classified 92.5% of the training set and correctly predicted the bitter almond character of 24 out of 25 test molecules having a chemical structure similar to that of the studied compounds. As mentioned above, the incorrectly classified test compound was 3-methylnitrobenzene.

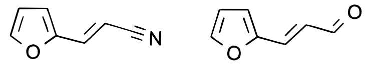
Outliers are often ignored in SAR studies, particularly when there is doubt concerning the accuracy of the measured biological activity. However, if the latter is reproducible, compounds such as 3-methylnitrobenzene, which exhibit unique biological activity may provide vital clues about the structural requirements for that biological activity. One possible explanation which could be offered for the underprediction of 3-methylnitrobenzene is based on the relative disturbance of the electronic properties of the nitro group by *ortho*-, *meta*-, and *para*-alkyl substituents. An alkyl group in any of these three positions will increase the electron availability over the aromatic nucleus by virtue of its inductive effect. However, for *ortho* and *para* substituents the electron-donating effect can also be transferred to the nitro group, as shown by the hybrid forms in Figure 15, although the hyperconjugation effect of the *ortho*-alkyl group is more difficult to estimate because of the possible partial loss of coplanarity between the nitro group and the aromatic ring. The lack of hyperconjugation in 3-methylnitrobenzene means that the electronic properties of the nitro group will more closely resemble that of nitrobenzene itself and this could be why they smell very similar. This effect is also seen in the benzaldehyde series, but to a lesser extent. 3-Methylbenzaldehyde is closer in odor to benzaldehyde than either the 2- or 4- methyl derivatives. In the higher homologues the detrimental effect of increased size outweighs the electronic effects and therefore the benzaldehyde-likeness of the 2-, 3-, and 4-alkyl-substituted benzaldehydes and nitrobenzenes are comparable.

Boelens[112] investigated a much wider range of bitter almond odorants. Some representative examples are provided in Figure 16. From over 100 compounds he concluded that 80% meet the following requirements: (1) The essential functional groups are electron-attracting and also negatively mesomeric. (2) The monosubstituted benzene derivatives have dipole moments between 2 and 4 Debye units. (3) A benzenoid (phenyl) or a pseudo-benzoid (furyl, thionyl) system gives the most characteristic odor. (4) Substitution of the aromatic nucleus with relatively small atoms/groups does not disturb the odor. (5) An aromatic nucleus is not necessary; cyclenic and olefinic structures can also have a bitter almond odor. (6) When a single double bond is conjugated with the functional group the bitter almond note is promoted. However, the introduction of more conjugated double bonds in nonaromatic systems diminishes the odor. (7) In olefinic compounds the molecule's profile should be isosteric with an aromatic nucleus.



23 24 25 26 27

Figure 16. Representative bitter almond odorants used in Boelens' study.



28 29

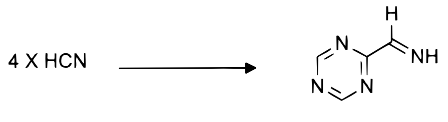
Figure 17. Anomalies to Buchbauer's vinylogue principal for cumin odor.

Boelens[66] subsequently attempted to find a relationship between the physicochemical parameters of 16 of these compounds and their bitter almond odor using the following formula (eq 3):

$$\text{odor quality} = F(\log P) + F(E) + F(S) + C \qquad (3)$$

where P is partition coefficient (hydrophobic parameter), E is $\Delta I/1000$ (electronic parameter), and S is mol volume/100 + width/height (steric parameter). The electronic parameter, ΔI, is the difference in Kovat's gas chromatography retention indices using a polar and a nonpolar stationary phase. ΔI was considered to be proportional to the electron donor/acceptor ability and to the polarizability of the molecule. By using multiple linear regression analysis a correlation coefficient of 0.95 and a standard deviation of 0.65 were obtained. The most significant parameters were log P and S.

The structural modifications required to shift the bitter almond odor to cinnamic−floral in character were investigated by Buchbauer *et al.*[113] in 1993. Thirty-four compounds were prepared and their odors subsequently assessed. A large number of these compounds belonged to the β-nitrostyrene family. They concluded that the extension of the functional group, directly bound to the aromatic system, by insertion of an ethylene unit generally shifted the odor from bitter almond to cinnamic, floral, and spicy (an observation which has been well established for years in the benzaldehyde, cinnamic aldehyde series). This vinylogue principle was, according to the authors, only contradicted by nitrile **28** and aldehyde **29**, both of which were described as having some benzaldehyde character (Figure 17). These materials were prepared by the condensation of furfural with cyanoacetic acid and acetaldehyde respectively. It is therefore possible that the condensation products



30

Figure 18. Klouwen's postulated tetramer.

contained trace amounts of furfural (23, Figure 16), which is itself a strong bitter almond odorant. This again highlights the importance of determining organoleptic purity when working on structure−odor relationships. Buchbauer also concluded that the addition of a nonplanar methyl group at the α position of an α,β-unsaturated compound leads to a more green scent.

The transition in odor from bitter almond to cumin was shown by Wright[114] to correlate with the pattern of frequencies observed in the far infrared. He concluded that the bitter almond odor was associated with a pattern of three frequencies near 175, 225, and 345 cm^{-1}, while the cumin odor correlates with a partly overlapping pattern made up of frequencies at 175, 265, and 310 cm^{-1}.

There is one notable exception to all of the above bitter almond models and that is hydrocyanic acid (HCN). Klouwen,[115] however, suggested that if hydrocyanic acid was tetramerized, the resulting triazine derivative **30** (Figure 18) would conform to the above structural requirements. To date, the formation of this material has not been confirmed. Other workers believe that anosmia for HCN suggests that there are two receptor sites corresponding to the smell of bitter almond; one of the HCN type and one of the benzaldehyde type.

Since HCN and benzaldehyde are always produced together in nature, Sell[116] asks whether the correlation in odor between these two materials could be the result of learning at higher levels in the brain/neuron system rather than events at receptor level.

C. Camphoraceous

The camphoraceous odor is fairly common in everyday life and is represented by products such as vapor rub and older versions of moth repellent. The ingredient responsible for the characteristic odor of these products is the bicyclic ketone, camphor (**32**), which is obtained naturally from camphor wood oil or synthetically from pinene.

The camphoraceous odor is by no means restricted to ketones. In fact, this class of odorants is somewhat unique. It is the only odor area where there appears to be no need for specific chemical functionality. This is illustrated by the four examples in Figure 19: at one extreme there is a hydrocarbon with no chemical functionality and at the other extreme a compound containing functionality which is usually associated with unpleasant odors (viz., nitrogen, phosphorous, and sulfur). The only common structural features of these four examples are their molecular shape and size. Amoore[117] was the first to point out that they are roughly spherical or egg-shaped with a diameter of approximately 7 Å.

One explanation for the observation that both nonpolar and polar molecules can possess strong camphoraceous odors was suggested by Beets.[118] He considered that the interaction of an odoriferous molecule with the receptor system was characterized by both the affinity of the molecule to the receptor surface and its efficacy, that is the ability of the molecule, when absorbed, to trigger a stimulus. Beets believed that the affinity was mainly determined by the functional group or groups and the efficacy by the profile and orientation of the molecule. Hence his use of the term "profile-functional group concept". Beets postulated that a high affinity and a well-defined odor are associated with compounds which contain only one, easily accessible functional group. The reason being that in such cases practically all of the molecules would be found in one strongly favored orientation at the receptor surface. When the molecule has more than one different functional group or a sterically hindered functional group the randomness of orientation increases. This in turn results in highly unselective interactions and a perceived complex odor. Beets pointed out that spherical molecules, such as the camphor-like odorants, will have the same profile in any orientation. Thus there is little difference between the statistical profile of a population of rigid spherical molecules of a saturated hydrocarbon contacting the epithelium in a random orientation and that of a population of spherical, rigid polar molecules in highly specific orientations.

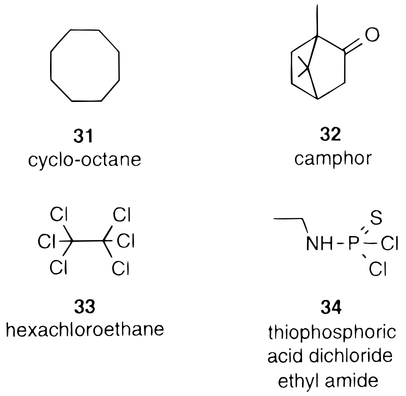


Figure 19. Compounds with a camphoraceous odor.

Intuitively one would expect that this unique class of odorants must contain vital clues about the mechanism(s) of olfaction and that as such it is an extremely important odor area for SAR work. Unfortunately because this class lacks the economic interest of other odor areas such as musk, it has received less attention.

The most extensive camphor SAR study was carried out by Amoore in the 1960s.[117] Using molecular models of rigid camphoraceous compounds Amoore constructed a clear plastic model of the complementary hypothetical receptor site. This receptor site was defined as the smallest basin into which all the rigid camphoraceous molecules could fit; it was an oval basin approximately 9 Å long, 7.5 Å wide, and 4 Å deep. For comparison the average molecular dimensions of the 21 rigid compounds were also determined. The molecular length was found to be 7.7 ± 0.7 Å, the molecular width 6.0 ± 0.4 Å, and the molecular height 5.3 ± 0.4 Å. Amoore suggested that 2-nitroso-2-methylpropane, which by itself would be far too small to fill the camphor site, may dimerize with a second molecule, as is the habit of aliphatic nitroso compounds, to achieve the necessary size and shape. Amoore also developed hypothetical receptor sites for four other odor characteristics—ethereal, musky, floral, and minty. He subsequently assessed the closeness of fit of 40 different odorants in each of these site models. The closeness of fit was quantified by measuring the volume of water displaced from the site by the molecular model. The proportion of the molecular volume left protruding above the water level was also taken into consideration when determining the degree of complementarity between each molecule and each site. For each odor character the correlation between molecular shape, as determined by the site-fitting method, and odor quality was assessed by plotting the complementarity site values against the odor-similarity scores. The results were very disappointing.

As Amoore himself pointed out, the major drawback with the site-fitting method is that a fundamental assumption about the receptor mechanism has to be made, that is that the olfactory receptor system actually recognizes a given molecular shape by testing its fit into a rigid open receptor site of more or less complementary shape. In order to avoid making such assumptions Amoore focused on the actual shapes of the molecules. For each odor class under investigation he chose a standard against which to compare both the shape and the odor characteristics of other odorants. The camphoraceous standard was 1,8-cineole. Similarity in shape was determined using Amoore's "shadow-matching method". Three silhouettes of each molecular model were produced. The orientation of the molecule during the generation of these silhouettes was determined by the shortest and longest axis of the model. The silhouettes of each compound were superimposed onto the corresponding silhouettes of the standard molecule according to their center of gravity and major axis. The similarity between molecular silhouettes was assessed by measuring the difference in length of corresponding radial lines (36 per silhouette). The average difference in radii length for the three silhouettes was used to calculate the similarity in shape of each compound with that of the standard compound. Correlations between the shape similarity index and the odor similarity scores were considerably better than those of the site-fitting method. The correlation coefficient (r) for the camphoraceous odor class was 0.63 compared with a value of 0.20 for the site-fitting method. When the data set was extended to 107 odorants a correlation coefficient of 0.56 was obtained.

Chastrette[119] introduced the shape factor SF to quantify molecular shape. He obtained the shape factor from measurements of the axes of the smallest ellipsoid in which a molecular model could be circumscribed. For example, if a, b, and c are the values of the axes of the ellipsoid, SF is given by eq 4 and takes a value of 1 for a sphere:

$$\mathrm{SF} = \frac{bc}{a^2} \tag{4}$$

Chastrette[120] used this shape factor as one of his parameters in the development of a camphoraceous discriminant function, that is a linear combination of molecular properties which allows one to predict whether or not a molecule will have a camphoraceous odor. First of all he defined a camphoraceous indicator variable which took a value of 1 for compounds with a camphoraceous odor and value of -1 for compounds with completely different odors. He then used a data set of 98 compounds, half of which were camphoraceous in odor, to derive a range of discriminant functions by multiple linear regression. The discriminant function (DF) which was found to have the best discriminating ability contained two parameters: molar volume (MV) and the shape factor (SF) (eq 5). The relative contribution of these two parameters to the discrimination was 20% and 80% respectively.

$$\mathrm{DF} = 0.0116(\mathrm{MV}) + 3.297(\mathrm{SF}) - 3.075 \tag{5}$$

$$n = 96 \qquad r = 0.813$$

Equation 5 was subsequently used to calculate the DF value of each compound. If the value of DF was positive the compound was classified as a camphoraceous odorant and if the value was negative the compound was classified as non-camphoraceous. Only seven of the 98 test compounds were misclassified and all but one of these had low DF values, that is to say they fell close to the boundary line between the two classification groups. This was also clearly evident in a two-dimensional plot of shape factor versus molar volume. In this plot the two groups of compounds were separated by a straight line which corresponded to a DF value of 0. As with any discriminant model, the level of confidence in a prediction about the activity of a compound which lies close to the boundary line is low. The confidence level increases as the compound lies further away from the boundary line. Indeed, Chastrette observed that there was some correlation between the magnitude of the DF value and the extent of camphoraceous character, even though he had originally assigned a value of $+1$ to all camphoraceous materials including those which are described in the literature as having faint camphoraceous notes. He pointed out that the five compounds with regression recalculated DF values of >1.5, all have very pronounced camphoraceous odors. They are 1,8-cineole, camphor, adamantane, fenchone, and borneol. It is interesting that the strongly camphoraceous odorant, cyclohexanol, was the only camphor-smelling material to be misclassified (DF $= -0.214$).

In addition to the above steric parameters, Chastrette also investigated the use of parameters which were related to the polarity of a molecule (i.e. refractive index and molar refraction) and to its hydrophobic/lipophilic nature (the logarithm of the octanol/water partition coefficient). All three parameters were found to be insignificant in discriminating between camphoraceous and non-camphoraceous compounds.

Chastrette[121] has recently described the structure of 45 camphoraceous alcohols, having the common skeleton RRCOHCRRCRR, using the van der Waals volume of the six R substituents. He has used this series of compounds to study the potential of neural networks in the calculation of odor thresholds. The data set was also extended to include aliphatic alcohols with fruity odors and this extended data set of 99 molecules was used to evaluate the use of neural networks in the development of a classification model. Although neural networks have found widespread application in other QSAR fields there have been relatively few publications concerning their use in the field of olfaction.

Neural networks attempt to mimic the functions of the human brain and as such consist of layers of interconnected neurons. A common number of layers is three. The first layer contains input neurons which, in this example, are the van der Waals volumes of the six substituents. The last layer contains output neurons, which are, in essence, the target property for each compound in the training set (i.e. odor threshold values or a numerical indicator representing whether or not a compound is camphoraceous or fruity). The hidden layer performs a mathematical function on the input data. The weighting applied to this function is continually modified by training the network until transformation of the input data produces an output which is as close as possible to the target values. A summary of the principles behind neural networks and their use in the analysis of chemical data is provided by Livingstone.[122]

Chastrette found that the network could correctly estimate the odor thresholds of 91% of the compounds used to derive the model. However, one of the best ways of evaluating the predictive ability of a model is by cross-validation (or the leave-out procedure). This involves rederiving the model using, for example, only 90% of the compounds in the data set and then using the new model to predict the activity of the omitted compounds. This process is repeated until every compound has been omitted once. Using this procedure only 74% of the odor thresholds were correctly estimated.

The discrimination model correctly classified all of the camphoraceous smelling alcohols and 95% of the fruity ones. The predictive ability for the two odor characteristics was estimated by cross-validation to be 95% and 74% respectively. The results are somewhat poorer for the fruity alcohols because they tend to have longer and more flexible molecules, whereas camphoraceous alcohols have short and highly branched molecules. Consequently, for improved classification of the fruity character, one would need to consider different conformational arrangements and use, as input to the neural network, descriptors which could discriminate between the various conformations (see the Compass technique, section IV.G.4).

In summary, the work of Chastrette and Amoore points toward a structure−camphoraceous correlation which is strongly shape dependent. Interestingly, in our experience at Quest International Amoore's shape and size criteria for camphor odor is the most universally applicable structure−odor correlation that we know. However, there does appear to be at least one exception to this rule and that is the replacement of the methylene bridge of homocamphenilone (**35**) by an oxygen atom (Figure 20).[123] The addition of this second, rather exposed, functional group results in complete destruction of the camphoraceous odor **36** whereas replacement of the methylene CH_2 unit with either ethylene **37** or propylene **38** has no dramatic effect on the odor. One possible explanation for this is the difference in hydrophobicity between **36** and **37** and **38**. Perhaps, the relationship between the structure and odor of camphoraceous materials is not as straight forward as one is first led to believe.

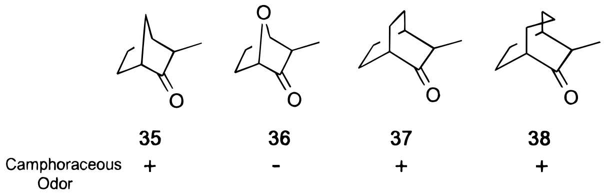


Figure 20. The effect of replacing the methylene bridge with either oxygen, ethylene, or propylene on the odor properties of camphenilone analogues.

D. Floral

Floral odors are generally appreciated by everyone. This is exemplified by the popularity of floral fragrances, particularly in the field of feminine fine fragrances, from the beginning of the perfumery industry until the present. Some highly successful perfumes in this area include Chanel 5 (Coco Chanel, 1921), Joy (Patou, 1935), L'Air du Temps (Nina Ricci, 1948), Eternity (Calvin Klein, 1988), and Pleasures (Estée Lauder, 1995).

Although a wide range of floral notes are used in perfumery, by far the most important are rose, jasmine, and lily of the valley. It is interesting that detailed structure−odor relationships have only been carried out in two of these odor areas. The third, rose, has received very little attention. The reasons for this are 3-fold. Firstly, the perfumer has at his disposal an excellent range of stable and cheap synthetic substitutes and secondly, rose is a complex odor. In addition rose odorants are conformationally flexible molecules and thus difficult to model.

Considering the wide variety of floral odors it is difficult to believe that there exists a relationship between the chemical structure of floral odorants in general. After all, generic odor descriptors such as floral, fruits and wood have only originated because of our association with the natural products. Nevertheless there have been a few SAR studies encompassing odorants from different floral families.

Kier[110] compared the odor of 16 floral compounds to that of 3-hydroxy-3-methyl-1-phenylpentane using, as he did in his study of bitter almond, molecular connectivity. He found that there was a significant correlation between the odor similarities and the zero-order connectivity index (${}^0\chi$), a parameter which reflects the size of the molecule and the degree of branching (eq 6):

$$\text{odor similarity} = 3.12e^{-1.66({}^0\chi - 9.51)^2} + 3.43 \qquad (6)$$

Using a qualitative approach Boelens[112] suggested that the structural features for a floral odor are (1) the presence of a substituted medium-sized ring or

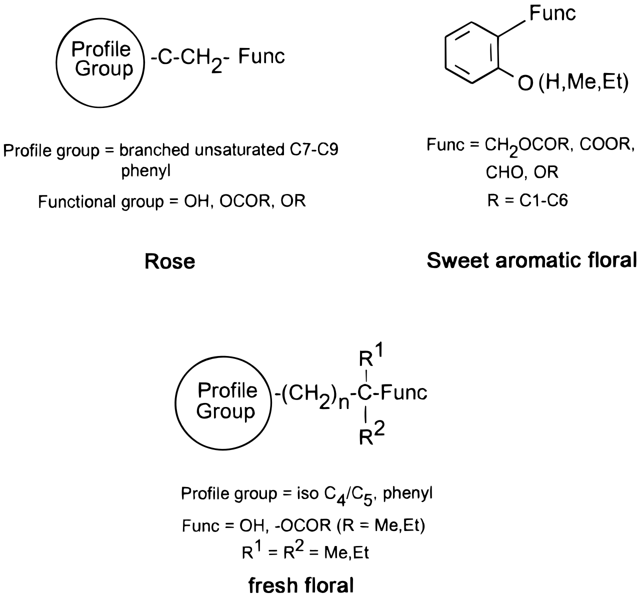
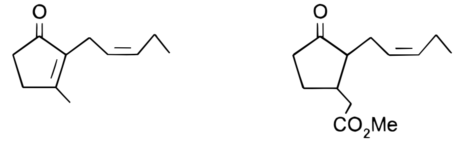


Figure 21. Boelens' floral rules.



39 40

Figure 22. Character impact components in jasmine oil.

an isosteric structure and (2) a carbon chain (C2 to C8) possessing an alcohol, carbonyl, ester, or ether functional group.

By modifying these rules Boelens[124] was also able to define more specific requirements for individual floral types (fresh-bergamot-like, rose, violet, sweet-aromatic, lily of the valley, and jasmine). Some of these are illustrated in Figure 21. His suggestions for jasmine and lily of the valley are considered in more detail in the following sections.

1. Jasmine

Jasmine absolute is very expensive and costs thousands of pounds per kilogram. This high price is primarily due to the large number of jasmine blossom heads (5 million) required to produce 1kg of oil and the labour intensive nature of the picking process. Out of the 250 or more components present in the extract only two have been shown to have odors characteristic of jasmine: jasmone (**39**) and methyl jasmonate (**40**) (Figure 22). These materials can now be prepared by a wide range of synthetic routes and cost £300−500/kg.

To aid the discovery of cheaper, more readily available alternatives chemists have again turned to structure−odor correlations. In 1938 Werner[125] suggested that for a jasmine odor the following criteria must be met: (1) A 5- or 6-membered cyclic ketone must bear an alkyl group in the α-position. (2) The total number of C atoms should be between 9 and 15, with 11 being optimum. (3) Ketones with straight chain alkyl groups have a better jasmine odor quality than those with branched chains.

In addition to the cyclic ketones, Boelens[112] also considered open-chain jasmine chemicals such as α-pentylcinnamic aldehyde. He concluded that the characteristic jasmine profile was determined by the presence of three different groups around a central carbon atom. These consist of a strongly polar group (C═O), an alkyl side chain having 5 or 6 C atoms, and a weakly polar group that can vary considerably in structure (e.g. carboalkoxy, lower alkyl, or phenyl group) (Figure 23).

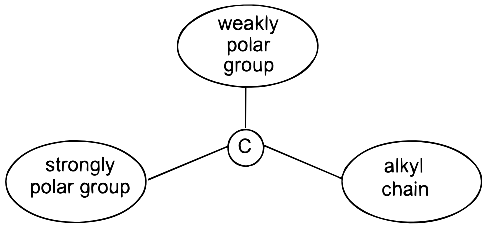
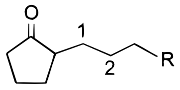


Figure 23. Boelens' jasmine model.



41

Figure 24. The effect of modifications on the alkyl side chain to jasmine odor of cyclopentanones.

Boelens[126] also quantitatively evaluated the odor similarity of 16 jasmine compounds and found that the odor quality was linearly related to molecular weight and the molecular connectivity index (χ^v), the latter of which reflects the degree of branching (eq 7).

$$\text{OQ jasmine} = F(\text{MW}) + F(\chi^v) + C \qquad (7)$$

$$r = 0.94 \qquad s = 0.80$$

Modifications of the alkyl side chain and the effect that these changes had on the odor of jasmine were explored by Sell and Dorman.[127] They synthesized a range of cyclopentanones containing branched and cyclic side chains in the 2 position. Their findings are summarized below:

(1) 2-*n*-Alkylcyclopentanones (**41**, Figure 24) exhibit predominantly jasmine odors if the chain contains 5, 6, or 7 carbon atoms.

(2) A substituent on the first carbon of the side chain (position 1) destroys virtually all of the jasmine character.

(3) A substituent on the second carbon atom (position 2) has the effect of replacing the jasmine character by rose.

(4) Substituents further down the chain have relatively little effect on the odor.

(5) 2-Alkylcyclopentanones having short, highly substituted side chains are camphoraceous because they fulfill the size and shape requirements postulated by Amoore for this odor.

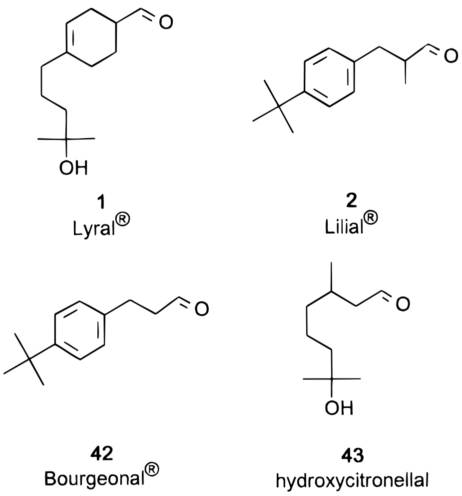
These observations were rationalized as follows. A substituent on position 1 obstructs one side of the C═O group thus reducing its accessibility as far as any receptor is concerned. This could account for the loss of impact and the destruction of the jasmine odor. In the case of substitution on the second carbon atom it was suggested that steric interaction with hydrogen atoms attached to C2 and C3 of the ring distorted the conformation of the side chain thus giving rise to a molecule with a different overall shape and odor character.

A new class of jasmine odorants was identified by Sell and Cairns[128] during their investigation into structure−odor correlations of methyl substituted aliphatic nitriles. They found that 2-methyl derivatives with 8−12 carbon atoms in the main chain possessed pronounced florality which was mainly of the jasmine type. In contrast the unsubstituted nitriles were harsher with lactonic, aldehydic, and nitrile character while the 3-methyl substituted nitriles had fresh, citrus, and green notes superimposed on a jasmine background.

2. Lily of the Valley (Muguet)

Since flowers from the lily of the valley (muguet) plant are very small and difficult to extract, it is impossible to produce a blossom oil from this plant. In addition, no component with the characteristic muguet odor has yet been isolated from the plant.[129] Therefore, perfumers have to rely on synthetic substitutes, such as Lyral (**1**), Lilial (**2**), Bourgeonal (**42**), and hydroxycitronellal (**43**), to create this odor type (Figure 25). However, the odor of these materials is somewhat heavier than that of the living flower, which is soft and quite roselike, but because of their widespread use in perfumery the consumer and also the perfumer now use the term lily of the valley to describe odors which are similar to the odors of these aroma chemicals rather than to the odor of the flower.

The aldehydic muguet ingredients were among the first to be discovered and are still highly valued in perfumery today. Since all of the early muguet odorants were aldehydes, the presence of the aldehyde functional group was believed to be a prerequisite for a lily of the valley odor. Other structural requirements, although not universally applicable, were considered to be[129,130] (1) a relatively high electron density around the third carbon atom (O−C3, C3=C, C3−C=C), (2) the presence of branched alkyl groups, cycloalkyl groups, or a benzene nucleus in the middle part of the molecule, and (3) at the opposite end of the molecule to the aldehyde function, a bulky group, sometimes containing an essential hydroxyl group which promotes and modifies the odor.



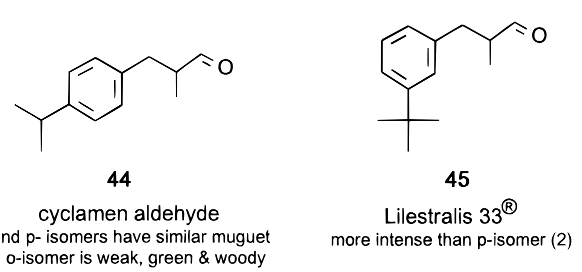
1 Lyral®

2 Lilial®

42 Bourgeonal®

43 hydroxycitronellal

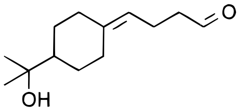
Figure 25. Synthetic muguet odorants.



44 cyclamen aldehyde
m- and p- isomers have similar muguet odor; o-isomer is weak, green & woody

45 Lilestralis 33®
more intense than p-isomer (2)

Figure 26. Relative odor characteristics of positional isomers.



46

Figure 27. Boelens' new odorant.

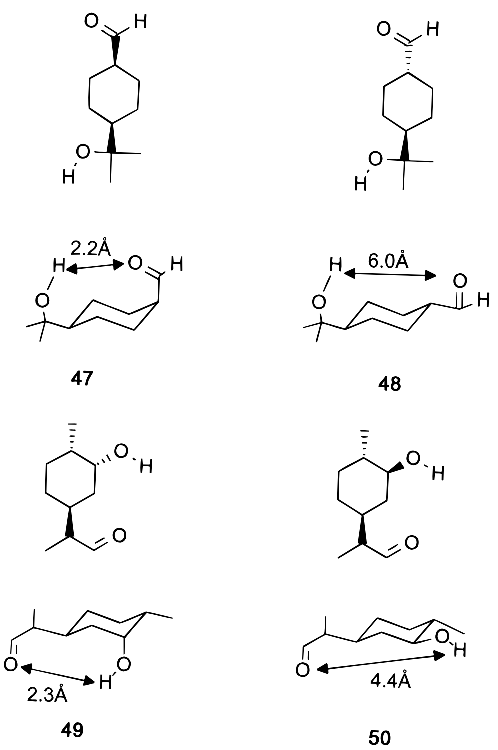
Berends and van der Linde[131] evaluated the floral character of 25 phenylpropanals. They concluded that analogues bearing an isopropyl, *tert*-butyl or *tert*-amyl group in either the *para* or *meta* position had odors which were reminiscent of cyclamen flowers. If the branching in the aromatic substituent is further removed from the aromatic nucleus, such as in the isopentyl or neopentyl analogues, the cyclamen character diminishes and the odor becomes more muguet. The introduction of an alkyl substituent in either the α or β position of the aldehyde chain causes a decrease in odor intensity, with the β substituent having the greatest detrimental effect. For example, Bourgeonal (**42**) is 2−4 times stronger than Lilial at the same concentration.[129,132] In the case of cyclamen aldehyde (**44**, Figure 26) it was concluded that there was little difference between the odor character and odor intensity of the *meta* and *para* isomers. The *ortho* isomer, on the other hand, was completely different, having a weak green-woody odor. In the Lilial series it has been claimed[133] that the *meta* isomer, Lilestralis 33 (**45**, Figure 26), is more intense than the *para* isomer (Lilial, **2**).

Boelens[126] quantified the odor quality of 16 muguet aldehydes by comparing their odor against that of a given reference standard. He then used this data to derive an equation (eq 8), which correlated the odor quality to molecular weight (MW) and the Kier connectivity index (χ^v), a measure of the extent of branching. On the basis of this work Boelens designed a new muguet compound **46** (Figure 27), which when made, did indeed have excellent olfactive properties.

$$\text{OQ muguet} = F(\text{MW}) + F(\chi^{v}) + C \qquad (8)$$

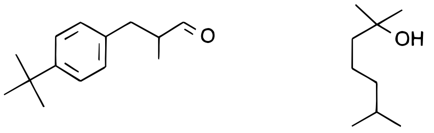
$$n = 16 \qquad r = 0.92 \qquad s = 0.9$$

The presence of two functional groups, as suggested in rule 3 above, was the basis of Ohloff's[134] bifunctional concept for odorants. He postulated that in some classes of odorants, a H-donor and H-acceptor must be separated by a distance of less than 3 Å in order for the compound to be odoriferous. Ohloff used this distance criterion to explain why, in certain hydroxycarbonyl compounds, only one diastereoisomer possesses the muguet odor (Figure 28). For example, by examining molecular models he claimed



47 **48** **49** **50**

Figure 28. Bifunctional molecules considered by Ohloff.



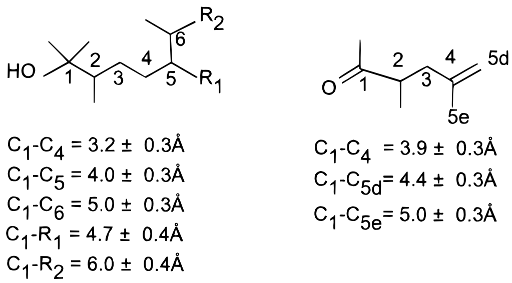
2 Lilial®

51 Freesiol®

Figure 29. Two examples of exceptions to postulated muguet rules.

that the distance between the two groups in compound **47** was 2.2 Å, but about 6 Å in the inactive *trans* isomer **48**. Similarly for compound **49** the distance was found to be 2.3 Å but 4.4 Å for its odorless diastereoisomer **50**. In the case of the commercially available Lyral (**1**), Ohloff states that if the hydrogen donor function is lost by replacing the hydroxyl group with either hydrogen or a H-acceptor such as OMe or OAc, the resulting compounds are odorless. Conversely, the carbonyl group can be replaced by other electronegative H-acceptor groups (e.g. acetals) with no significant effect on odor.

There are, however, well-known lily of the valley odorants which do not obey either of the above models (Figure 29). For example Lilial (**2**) is bifunctional but lacks a hydrogen donor and Freesiol (**51**) contains only one functional group, an alcohol moiety. Indeed, in more recent years attention has been focused toward the discovery of non-aldehydic muguet materials because of the instability associated with certain materials from this chemical class. Pelzer[133] suggested that there were two classes of lily of the valley odorants; those which have an OH group and those with a carbonyl group. The two types were claimed to possess different odor profiles with the carbonyl compounds exhibiting, in addition to the muguet aspects, lime blossom notes. On the basis of both the odor profile of Lyral (**1**) and the fact that replacement of the hydroxyl group results in a loss in the lily of the valley odor, Pelzer classified Lyral as an alcohol muguet odorant. These two classes also exhibited very different substitution patterns around the key functional group (Figure 30).

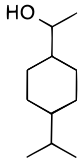


C_1-C_4 = 3.2 ± 0.3Å
C_1-C_5 = 4.0 ± 0.3Å
C_1-C_6 = 5.0 ± 0.3Å
C_1-R_1 = 4.7 ± 0.4Å
C_1-R_2 = 6.0 ± 0.4Å

C_1-C_4 = 3.9 ± 0.3Å
C_1-C_{5d} = 4.4 ± 0.3Å
C_1-C_{5e} = 5.0 ± 0.3Å

Fragment 1 **Fragment 2**

Figure 30. Pelzer's muguet fragments.



52

Figure 31. Mugetanol.

Pelzers' analysis of 73 alcohols produced the following rules for fragment 1:

(1) C1 is substituted by one to three alkyl groups, ideally three, provided that the hydroxyl group is not overshadowed too strongly by steric hindrance.

(2) C2, C5, and to a lesser extent C6 and C7 are substituted by a single alkyl group (ideally methyl). Dimethyl substitution generally has a detrimental effect.

(3) Where a double bond is present it should preferably be at C4 or C6. A double bond between C3 and C4 or, to a lesser extent, between C2 and C3, generally has a negative influence on the odor.

For fragment 2 it was found that:

(1) An aldehyde is always better than a ketone function.

(2) C2 should be substituted by one or two methyl groups, preferably one.

(3) C4 should be alkyl substituted. A double bond at C4 is particularly advantageous, and may also be part of an aromatic system.

The use of these models led to the synthesis of a series of interesting new fragrance ingredients, the most notable of which was Mugetanol (**52**, Figure 31).

In 1992 Pelosi *et al.*[135] discovered two tetrahydropyranyl ethers **53** and **54**, which they claimed had very similar odors to that of hydroxycitronellal **43**. A molecular profile comparison with hydroxycitronellal (**1**) and Lilial (**2**) indicated some similarity in shape, particularly in the hydrocarbon part of the molecule, supporting the observed odor similarity (Figure 32). Inspired by the discovery of a potentially new class of muguet odorants, Pelosi's group synthesized a much wider range of analogues in order to gain further insight into the relationship between chemical structure and the floral odor of alkoxycyclo ethers. They investigated the effect of the position and size of the substituent on the cyclohexane ring,

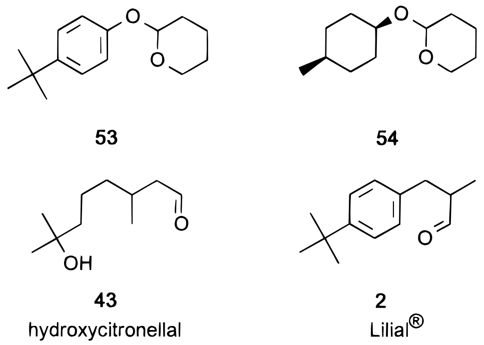


Figure 32. Comparison between the structures of the tetrahydropyranyl ethers of *p*-*tert*-butylphenol and *cis*-4-methylcyclohexanol (**53** and **54**, respectively), and those of hydroxycitronellal and Lilial.

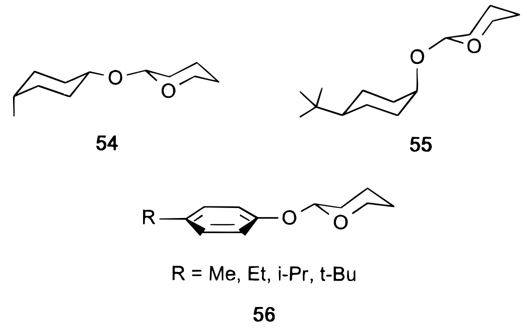


Figure 33. Effect of the alkyl substituent on the preferred conformation and shape of the THP ethers of 4-alkylcyclohexanols.

the replacement of the 2-tetrahydropyranyl group by the smaller 2-tetrahydrofuranyl ring[136] and the replacement of the oxygens with either sulfur[137] or carbon.

They found that the position of the methyl group on the cyclohexane ring did not affect the odor appreciably, with all of the derivatives having some floral character. However, increasing the size of the substituents in position 4 drastically reduced the odor intensity. I believe that this change in odor intensity is due to changes in preferred conformational arrangement. In the case of the *cis*-THP ether of 4-methylcyclohexanol **54**, the most stable conformation will have the ether linkage equatorial and the methyl group axial. As the size of the alkyl substituent increases, competition for the equatorial position is introduced until, in the *tert*-butyl analogue **55** the preferred conformation has the very bulky *tert*-butyl group equatorial and the ether linkage axial. The shape of the molecule is completely altered and the muguet odor destroyed (Figure 33). In contrast, the shape of the THP ethers of *p*-alkylphenols **56** will always be relatively flat and therefore the methyl, ethyl, isopropyl, and *tert*-butyl derivatives all possess floral odors.

The odor of the THF derivatives were markedly different from their THP homologues. Although the THP ethers are, in general, more floral than their corresponding THF derivatives, the reverse is true for 4-substituted cyclohexanols. Pelosi *et al.*[136] suggested that these differences could be due to the different orientations of the bonds in the THF and THP rings, giving rise to molecules of different shape.

In general, replacement of either one or both oxygens with sulfur resulted in the loss of the floral odor. The derivatives with two sulfur atoms had unpleasant odors while those with an endocyclic oxygen atom and an exocyclic sulfur atom were generally green and fruity. The floral character was retained in only two derivatives, both of which contained an endocyclic sulfur atom and an exocyclic oxygen atom. These results suggest that the exocyclic oxygen atom is important for a floral odor. However, oxygen/carbon replacement experiments contradict this. The floral odor is lost when either oxygen is replaced with a methylene group.

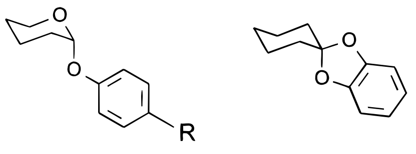


Figure 34. Design of spirane **57** guided by conformational comparisons with **56**.

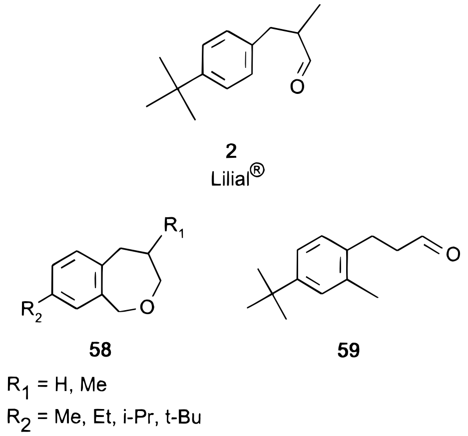


Figure 35. 1,3,4,5-Tetrahydro-2-benzoexpin derivatives (**58**) as conformationally restricted analogues of Lilial-type compounds and novel muguet aldehyde (**59**) discovered by Winter *et al.*

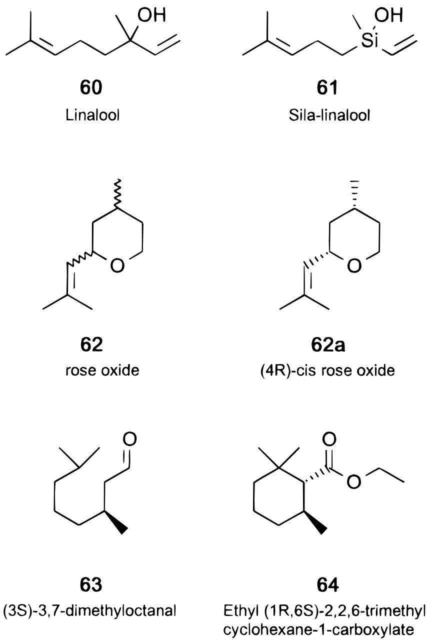
To further investigate the effect of stereochemical factors, Pelosi *et al.*[138] used the postulated active conformations of the floral THP and THF ethers to design a new series of more rigid molecules. They replaced the endocyclic oxygen with a methylene group and, in order to increase rigidity, added a bridging oxygen (Figure 34). When **57** was prepared by the condensation of methylcatchecol and cyclohexanone it was indeed found to possess the predicted muguet odor. Other closely related spirane analogues had odors ranging from geranium to green and fruity.

Winter *et al.*[139] have also investigated conformationally restricted analogues of known muguet materials. They synthesized a series of eight 1,3,4,5-tetrahydro-2-benzoxepin (**58**) derivatives as mimics for the folded conformation of Lilial (**2**) and related compounds (Figure 35). Since all of these products did not possess any lily of the valley odor the authors suggested that the active conformation of Lilial-type compounds is more likely to be with the aldehyde side chain extended. These findings are in agreement with the work of Pelzer *et al.*[133] who proposed that the distance between C1 and C4 should be 3.9 ± 0.3 Å. Winter used molecular modeling to show that aldehydes with a substituted side chain, such as

Lilial (**2**), preferred a "folded" conformation, while those with no substitution, such as Bourgeonal (**42**), favored an extended conformation. This again highlights the fact that the organoleptically active conformation of a compound is not necessarily the lowest energy one. However, steric factors are not the only important prerequisite for odor. Conversion of an aldehyde group to a cyclic ether will have a dramatic effect on the chemical reactivity and electrostatic properties of a molecule and it could be for these reasons that the 1,3,4,5-tetrahydro-2-benzoxepin derivatives do not exhibit the desired muguet odor. During the course of this work Winter *et al.*[139] also synthesized a range of novel phenylpropanal analogues having an extra methyl group in the ortho position. One of these new aldehydes **59** was described as having a Lilial-type odor.

3. Rose

The few recent investigations into the effect of structure on rose odor have been centered around specific ingredients. In linalool (**60**) and silalinalool (**61**) (Figure 36), it has been shown that the $(CH_3)_2C{=}CH$ group can be replaced by $(CH_3)_2C{=}N$ and $(CH_3)_2CH{-}CH_2$ with no significant change in odor qualities, while alteration of the alcohol functional group results in a dramatic odor change.[140] Sila derivatives of other fragrance ingredients have also been synthesized. In some cases the odor of the parent carbon compound is still discernible, whereas in others the odor is either destroyed or dramatically changed. Those examples where the odor of the sila analogue is similar to that of the carbon counterpart are interesting anomalies for the vibrational theories of Dyson, Wright and Turin. Wannagat[141] reviewed the odor properties of sila perfumes in 1984. Since then Wannagat *et al.* have synthesized and studied the odor properties of α-formylpropenylsilanes[142] and sila-β-ionone,[143] compared the odors of carbinols and silanols with those of thiocarbinols and silanethiols,[144] and investigated the effect of replacing quaternary carbon atoms with other group IV elements (Ge, Sn).[145] The germanium analogues were found to possess interesting fragrance qualities, whereas the tin analogues were found to be odorless. Presumably the loss in odor on going from germanium to tin is due to a decrease in volatility. Tang and co-workers, the other main research group in this field, have evaluated the odor properties of acetals from (trimethylsilyl)cyclohexenones,[146,147] (trimethylsilyl)cyclohexanones,[146] and 1-substituted 4-(trimethylsilyl)cyclohex-3-enols and their saturated analogues.[148]



60 Linalool
61 Sila-linalool
62 rose oxide
62a (4R)-cis rose oxide
63 (3S)-3,7-dimethyloctanal
64 Ethyl (1R,6S)-2,2,6-trimethylcyclohexane-1-carboxylate

Figure 36. Compounds possessing roselike odors.

Matsuda[149] synthesized and evaluated both the odor and environmental biodegradation properties of the four optical isomers of rose oxide (**62**). They concluded that it was the (4*R*)-*cis* isomer **62a**, with an odor threshold 100 times lower than that of the (4*S*)-*cis* form, which was predominantly responsible for the rose and green notes of the rose oxide mixture. The other isomers were shown to have additional fruity, herbal notes. They also concluded that the (4*R*)-*cis*-isomer is the most readily biodegradable isomer. They claim that more than 90% of the (4*R*) form was degraded after 28 days, whereas the (4*S*) form was not degraded at all.

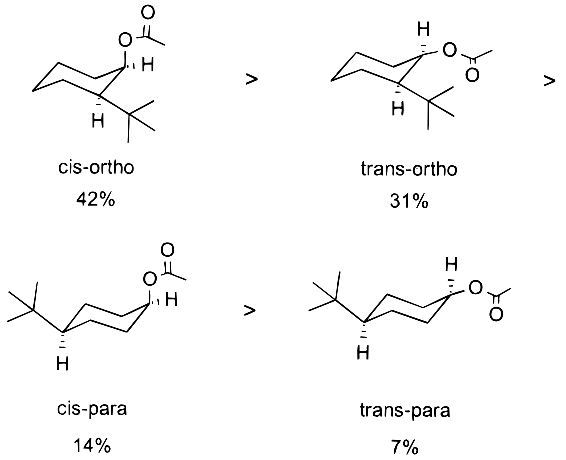
Yoshii *et al.*[150] studied and compared the ringlike conformers of (3*S*)-3,7-dimethyloctanal (**63**) with those of ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate (**64**). They found that the chain-type odorant could adopt two stable conformations which resembled conformations of the cyclic odorant. They postulated that these conformations could bind and stimulate the same odor receptor and that this is the reason why there is some similarity in the odors of these two materials. (3*S*)-3,7-Dimethyloctanal is described as having a floral odor with a sweet rosy note and ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate as having a clean sweet floral, fruity odor.[151] It is worth pointing out that the commercially available racemic mixture of 3,7-dimethyloctanal has a citrus, lemon, fresh green odor with a floral, lime-like note.[152]

E. Fruit

All chemists from their early studies in chemistry will remember reacting an alcohol with a carboxylic acid to produce a fruity smelling product—an aliphatic carboxylic ester. However, the ester functionality is not necessarily a criterion for fruity odor. Out of a list compiled by McGugan[153] of 85 fruity odorants, 41% were esters, 24% ketones, 9% aldehydes, 7% lactones, and the remaining miscellaneous. Methyl ketones in particular display a great similarity, in terms of odor, to the corresponding acetates.[154−156] Boelens[157] studied the neryl, geranyl, and citronellyl acetones, acetates, and ethyl ethers. In all cases both the acetone and acetate derivatives possessed fruity notes. For the neryl analogues, the ethyl ether was also described as fruity. He concluded that within this series structural changes in the terpenyl profile group had a greater effect on the odor character than changes in the functional group.

1. Esters

However, there is no doubt that the main group of fruity odorants are esters and, as a result, this class



cis-ortho 42%

trans-ortho 31%

cis-para 14%

trans-para 7%

Figure 37. The percent fruit score of the isomers of *tert*-butylcyclohexyl acetate.

of compounds has been the center of several SAR studies. Boelens[67] in 1983 rated the fruity odor aspect strengths of 106 esters against ethyl phenylglycidate and then attempted to correlate these ratings with features of the molecular structure by multiple regression analysis. He found that the odor intensity was significantly influenced by the nature of both the acid and alcohol part. The following rules for aliphatic esters were proposed:

(1) Aliphatic esters up to C8 are strongly fruity.

(2) Esters from alcohols C6−C10 and acids to C2 are moderately fruity.

(3) Esters from alcohols C6−C10 and acids C3−C5 are fruity.

(4) Esters from alcohols up to C10 and acids over C8 are not fruity.

(5) Esters from C3−C5 acids are fruitier than esters from C1−C2 acids which, in turn, are fruitier than esters from acids over C6.

(6) In general, fruitiness decreases with increasing molecular weight.

Following on from this work, Sell[158,159] investigated the effects of steric hindrance of the ester function and also the presence of unsaturation in its proximity for a series of aliphatic esters. A number of correlations were suggested:

(1) Unsaturation in the proximity of the ester function reduces the pear/peardrop character and adds green notes to the odor.

(2) Intense green notes are associated with *cis*-olefins and esters of acetylenic alcohols.

(3) The pear character of an ester is diminished when steric bulk around the ester function is increased. This effect is more marked when blocking is situated on the alcoholic portion of the ester.

When the isomers of *tert*-butylcyclohexyl acetate were evaluated it was found that, contrary to the above, the fruitiness increased with steric hindrance (Figure 37). However, the fruity character of these esters is distinctly apple. Therefore Sell concluded that it is not reasonable to search for a general fruity−structure relationship since the requirements for each individual fruity character are different. As Boelens[160] pointed out, in his review on the molecular structure and organoleptic quality of flavor ingredients, there can even be distinct subclasses within one fruit family. For example, a detailed study of the organoleptic quality of apples showed that there are at least three different types of apples and that the structural aspects of substances with different apple qualities are not very alike.

Each ester in Sell's data set had been quantitatively assessed against 51 standard odor descriptors by an expert panel. It is thus one of the few published data sets for which good reproducible quantitative odor data is available. This was just one of the reasons why I chose this series of compounds for my evaluation of the relative usefulness of three different QSAR techniques in understanding and predicting the odor properties of chemicals.[161] Upon the basis of Sell's conclusion that "apples are not pears" I restricted my study to those esters which had a fruit score predominantly made up from the pear/peardrop descriptor. The three techniques which were evaluated were regression analysis, principal component analysis, and a three-dimensional QSAR technique called CoMFA[162] (*co*mparative *m*olecular *f*ield *a*nalysis).

The regression analysis was attempted with the use of a range of structural descriptors. The combination of parameters which best accounted for the observed differences in the fruit score was eq 9.

$$\text{fruit score} = 94.4 - 37.8\upsilon_{\mathrm{R}} - 48.6\upsilon_{\mathrm{OR}} + 6.1L - 135L_{\mathrm{comb}} \quad (9)$$

$$n = 24 \qquad r^2 = 0.67 \qquad \text{cross-validated } r^2 = 0.50 \; F = 21.34$$

where υ_{R} is the Charton substituent constant for the alkyl group attached to C=O, υ_{OR} is the Charton substituent constant for the alkyl group attached to the ether O, L is the molecular length, and L_{comb} is the descriptor for the position of the ester group in the chain. The Charton parameter is related to measured rates of the hydrolysis of esters and as such is a measure of intramolecular steric effects around the ester group.[163,164] The larger negative coefficient of υ_{OR} means that steric hindrance around the ether oxygen atom has a greater detrimental effect on the fruitiness of the ester than steric bulk around the carbonyl group. These results are in agreement with the findings of Sell.[158,159] L_{comb} is a parameter which defines the relative position of the ester group in the aliphatic chain. As L_{comb} increases, that is as the ester group is placed toward the center of the chain, the fruity character is reduced. It was shown that log P could replace the role of length in the correlation QSAR because these two parameters are highly correlated. However, their physical interpretation in understanding structure−odor correlations is quite different. Molecular length could be associated with shape requirements for optimum interaction with the receptor system, whereas the balance between hydrophobicity and lipophilicity will affect the transport properties of a molecule across aqueous−lipid interfaces.

The same parameters were used in the principal component analysis. This four-dimensional data set was successfully reduced to a two-dimensional set. The resulting two principal components, each of which are linear combinations of all the original parameters, were used as the axes in a 2-D plot. Clusters of esters with strong, moderate, and weak fruity odor characteristics were obtained.

The CoMFA approach compares the steric and/or electrostatic fields of a set of molecules. These fields are measured by placing a hypothetical probe atom at regular positions around the molecule and at various locations, calculating the energy of interaction between the probe atom and the molecule. Any correlation between the fields and the biological activity is displayed graphically. In the case of the fruity ester data set it was concluded that electrostatic effects were unimportant. This is to be expected since all of the esters contained only one polar group, the ester group, and this group was superimposed. The ideal steric requirements for a fruit odor were shown to be the absence of steric bulk in the vicinity of the ether oxygen atom and steric bulk approximately five carbon atoms way from the ester group. However, one of the limitations of the CoMFA model for this data set was its inability to graphically represent that the most fruity esters have a long chain on one side of the ester group and a short chain on the other, and that it does not really matter which way round the ester linkage joins these two chains.

All three models were used to predict the fruitiness of four new esters. It was concluded that the CoMFA model, although best at explaining the observed variation within the training set, was restricted to predictions about the fruitiness of esters which were very similar in structure to those used to derive the model. The regression model, on the other hand, was much better at extrapolative prediction. This difference in predictive ability is believed to be due to the different methods used to quantify steric effects. Advantages of the Charton steric substituent constants include their relationship to measured rates of hydrolysis of substituted esters and their independence of the postulation of a single active conformation. Since the success of the CoMFA is strongly dependent upon the choice of the correct active conformation and upon the relative alignment of the individual molecules, it is anticipated that its use will be more applicable to the study of rigid molecules and closely related analogues.

Another group of esters for which detailed odor measurement data has been published is the acetates, propionates, and butyrates of a range of 1-(*p*-alkyl)phenylethanols.[165] The odor profile of these esters was defined using a set of 57 odor descriptors. It is interesting to note that despite the findings of Sell,[158,159] the odors of apples and pears were combined to produce one descriptor. The authors claim that the main odor characteristics of all the materials are similar. They are described as possessing fruity, flowery, woody, and pungent odors with minor rotten, mouldy notes. There is, however, no discussion about the more detailed differences in the odor profiles. It is clear from the tabulated odor profile data that changes in the *p*-alkyl substituent have a greater effect on the odor characteristics than changes in the acid moiety. For example, all three methyl derivatives have lemon, citrus, honey-like, sweet, aromatic, and parsley root notes which are absent in the *n*-propyl, isobutyl, and *tert*-butyl derivatives, while the *n*-propyl analogues have an extra terpenic note but lack the sharp and temperate-zone fruit characteristics found in the methyl, isobutyl, and *tert*-butyl derivatives. In addition, the acetates in each series have a much lower odor threshold than either the propionate or butyrate derivatives, with the latter two having fairly similar threshold values. However, these are thresholds based on solutions in paraffin oil rather than on air concentrations and thus may reflect volatility.

The effect of ring size on the odor threshold of a series of cyclic esters was studied by Takeoka[166] and co-workers. They found that increasing the ring size from cyclopropyl to cyclopentyl or cyclohexyl resulted in a 100-fold lowering of the odor threshold. However, on progression to the cycloheptyl and cyclooctyl analogues only a slight effect on the odor threshold was observed. The introduction of unsaturation into the cyclohexane ring was also examined. A double bond in the 3 position had little effect on the odor threshold, whereas a double bond in the 1 position resulted in a substantial loss in odor potency.

2. Miscellaneous

Grapefruit, passion-fruit, grape, melon, and blackcurrant odors are produced by certain sulfur compounds when present at very low concentrations. Indeed, volatile organic sulfur compounds are very important constituents for the flavor of food and beverages, not only in the area of fruit flavors but also, for example, in meat, bread, garlic, potato, beer, and coffee. Fruity accords are also very popular in perfumery. A few examples include the Dewberry range by The Body Shop, Fantasme (Ted Lapidus, 1992), Chiffon Sorbet (Escada, 1993), and Deci Dela (Nina Ricci, 1994).

At high concentrations volatile organic sulfur compounds generally have the unpleasant odors that chemists usually associate with sulfur materials. This dependence of odor quality on concentration makes it very difficult to carry out structure-activity studies on this group of compounds. Some general observations have been summarised by Boelens[167] in his review on the sensory properties of sulfur compounds. At high concentrations, lower alkyl thiols and mono-, di-, and trisulfides often possess sulfurous notes whereas bifunctional monosulfides and substituted thiophenes may have “olefinic” notes. In fact, as Boelens points out, the *cis* carbon−carbon double bond in *cis*-3-hexenol and *cis*-3-hexenyl acetate can be replaced by a sulfur atom with no significant effect on the odor profile. In terms of odor thresholds, tertiary thiols have values which are 300−3000 times lower than those of primary and secondary ones.

One small group of sulfur compounds which has been the focus of an SAR study is a series of four mercapto ketones and mercaptans[168] (Figure 38). All four materials were perceived as having the “catty” note of blackcurrant bud oil, which has always been of interest for the flavorist and, more recently, for the perfumer. Upon the basis of these observations, Polak[168] concluded that the tertiary mercapto amyl substructure is the important odor quality determining feature and this fits well with the observation

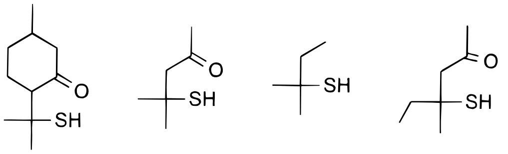
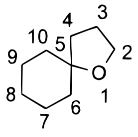


Figure 38. Thiols with the “catty” note of blackcurrant bud oil.



65

Figure 39. Common skeleton of the 1-oxaspiro[4,5]-decanes studied by van der Weerdt.

that all of the early known blackcurrant-smelling compounds were thiols. However, since the mid-1970s a number of materials have been discovered that do not contain a sulfur atom. The structural requirements for one such group of compounds were investigated by van der Weerdt.[169] He concluded that in order for 1-oxaspiro[4,5]decanes **65** to have a blackcurrant odor the furan ring should be of the dihydro type and bear a methyl group at C-2 and that the cyclohexane ring should be substituted at C-6 or C-7 and at C-9 and/or C-10 and be unsaturated between C-6 and C-7 (Figure 39).

F. Green

Compounds which are described in perfumery terms as having a “green” odor have been the focus of very few SAR studies. Perhaps the main reason for this is that green notes are difficult to define. Because of associations with color and nature, the term green denotes an odor which is reminiscent of green foliage such as leaves, stalks, and green vegetables, and the smell of freshly cut grass. The compound which is released when a lawn is mowed is *cis*-3-hexen-1-ol (**66**, leaf alcohol), and it was the introduction of this material and its derivatives in the 1960s which brought about a revolution in the use of green notes in flavors and fragrances.[170,171] The history, occurrence, preparation, and organoleptic properties of *cis*-3-hexen-1-ol and its derivatives have been reviewed by Bedoukian[172] and Clark.[171] An overview of their biogeneration is provided by Hatanaka *et al.*[173] Green notes can also been found in a range of other chemical families, including alkoxy-substituted pyrazines **67**, di- and trimethylcyclohexene carboxaldehydes **68**, undecatrienes **69**, phenylacetaldehydes **70** and some aromatic acetals, ethers, esters and alcohols (Figure 40). Reviews of green odorants and their use in perfumery have been provided by Morris,[170] Panten,[174] and Woerner.[175]

Studies into the relationship between green odor and structure have been confined to aliphatic alcohols and aldehydes. Bedoukian[176] investigated the effect of the position and geometry of the double bond on the odor of hexen-1-ols. He concluded that there was an appreciable difference in odor between the *cis* and *trans* forms of each alcohol with the *cis* forms being consistently sharper and greener and the *trans* forms more fatty. It is interesting to note that *n*-hexanol also has a fatty character and that this is presumably due to the similar geometry of the alkane and *trans*-alkene chains. With regard to the position of the double bond, he found that the most pleasant compound was *cis*-3-hexenol, followed by *trans*-3-hexenol and the 2-hexenols. The odor of the 4-hexenols was judged to be decidedly less attractive and that of 5-hexenol to be unpleasant. Hatanaka[177] quantitatively assessed the odor of these seven hexenols and their corresponding hexenals by rating the strength of 10 odor characteristics on a six point scale (0, just detectable; 1, very weak; 2, weak; 3, medium; 4, intense; and 5, very intense). The odor data was statistically analyzed using principal component analysis. The results suggest that as the double bond is successively moved down the chain from the 2 position to the 5 position the odor shifts from fruity, fresh, and sweet, through leafy and grassy green, and then insect-green and vegetable-like green, to oily-fatty and herbal. It was also apparent that hexenals with the same position and geometry of the double bond have very similar odor profiles to those of the corresponding hexenols, except that they are 10 to 1000 times more potent.

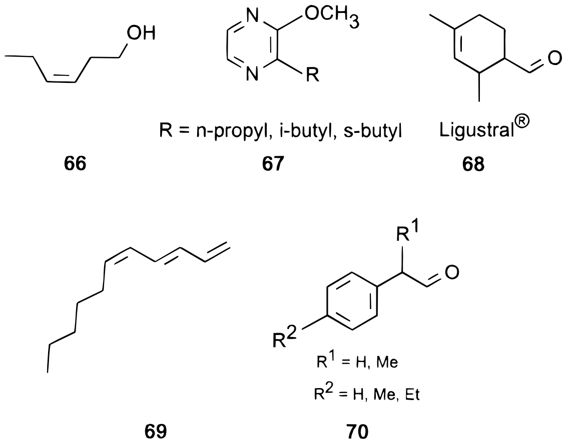


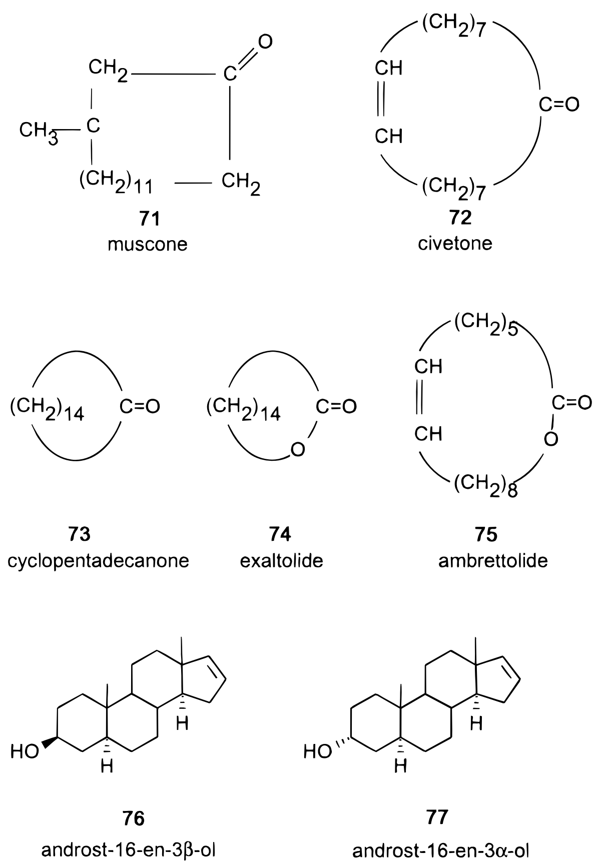
Figure 40. Compounds possessing green odors.

Vasil’ev *et al.*[178] prepared 47 C_5-C_{10} alkenols in their search for a potential substitute for *cis*-3-hexen-1-ol. They varied the carbon chain length, the position and geometry of the double bond, and the substitution pattern. The results were consistent with earlier findings that the green odor of *cis*-3-hexenol is predominantly found in C_6-C_8 alcohols which have a double bond in either the 2 or 3 position and that the green odor of the *cis* isomers is more pronounced than that of the corresponding *trans* isomers. It appears that the green odor of *cis*-3-hexen-1-ol still remains unsurpassable.

G. Musk

Musk odorants are very important perfumery ingredients both for their fixative properties and their characteristic odor quality, which is referred to as warm, sensual, animal, and natural. Indeed, in 1955, Carpenter[179] said that “There is hardly a perfume type, from the simplest of colognes to the most subtle and sophisticated of orientals, that does not benefit from the inclusion of some musk.”

Originally musks were obtained from natural sources belonging to both the animal and vegetable



71 muscone

72 civetone

73 cyclopentadecanone

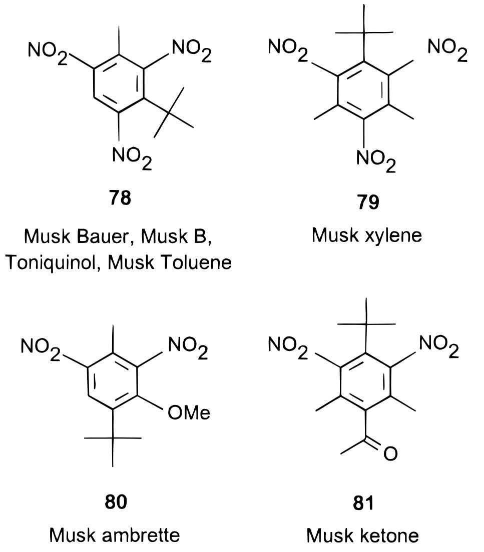
74 exaltolide

75 ambrettolide

76 androst-16-en-3β-ol

77 androst-16-en-3α-ol

Figure 41. Natural musks.



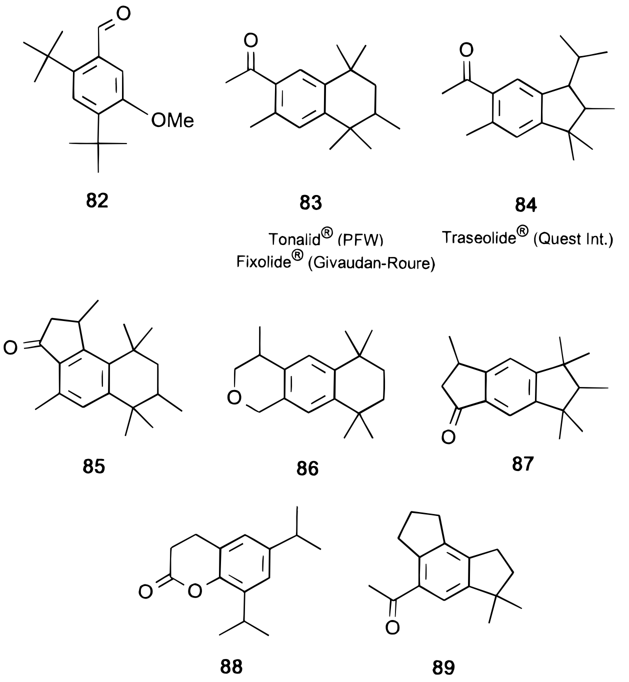
78 Musk Bauer, Musk B, Toniquinol, Musk Toluene

79 Musk xylene

80 Musk ambrette

81 Musk ketone

Figure 42. Nitro musks.



82

83 Tonalid® (PFW) Fixolide® (Givaudan-Roure)

84 Traseolide® (Quest Int.)

85

86

87

88

89

Figure 43. Examples of non-nitro musks.

kingdoms (Figure 41). Traditionally, muscone (**71**) was derived from the musk deer, civetone (**72**) from the civet cat, and cyclopentadecanone (**73**) from the Louisana musk rat. Nowadays, these materials are prepared synthetically. The vegetable kingdom, although containing a more limited number of musks, provides us with macrocyclic lactone musks, which according to many perfumers are superior in odor quality to the corresponding ketones. Cyclopentadecanolide (Exaltolide, **74**) is obtained from Angelica root and *cis*-7-cyclohexadecenolide (Ambrettolide, **75**) from Ambrette Seed Oil. A small group of natural steroid musks is also known. Two isomeric alcohols, androst-16-en-3*β*-ol (**76**) and androst-16-en-3α-ol (**77**), are found in lipid extracts from the seminal vesicle of pigs and also the saliva of boars. The steric configuration of the hydroxyl group has a strong influence on the odor; the 3α-derivative has an animalic musk-like odor whereas the 3*β*-epimer is practically odorless. The odor of the corresponding ketone, which as yet has not been detected in nature, is much stronger than the alcohols and urinous in character.[180] (For further details on the origin, the odor properties, and the synthesis of natural musks the reader is referred to the reviews of Mookerjee and Wilson,[181] and Wood.[182])

Serendipity has played an important role in the history of synthetic musks. In 1888 Bauer,[183] in the course of his research into the synthesis of explosives, made the surprising discovery that 2-*tert*-butyl-4-methyl-1,3,5-trinitrobenzene (**78**) has a fine musk odor. This stimulated further research and led to the subsequent rapid discovery of musk xylene (**79**), musk ambrette (**80**), and musk ketone (**81**) (Figure 42). The family of synthetic musks grew significantly to include nitrated derivatives of tetralin and indan. Some 60 years later, during the preparation of a number of isomers, homologues, and analogues of musk ambrette, Carpenter *et al.*[184] found that one of the precursors, 3-methoxy-4,6-di-*tert*-butylbenzaldehyde (**82**), had a musk odor which was closer in character to the macrocyclic musks than the nitro-type musks. Today their are examples of non-nitro musks derived from tetralin **83**, indane **84**, naphthindanone **85**, isochroman **86**, hydrindacenone **87**, coumarin **88**, and hydrindacene **89** (Figure 43).

Although the well-defined musk odor is found within four very different musk families, each one is governed by very tight structural criteria. Minor structural changes can cause complete destruction of the musk odor. Thus, musk is an odor area where there are examples of structurally different compounds with similar odor qualities and structurally similar compounds with different odor qualities. This creates a problem for the SAR worker. Some, on the basis of the observation that there are subtle odor differences between the different families, have assumed that there is more than one musk receptor and searched for correlations within a given group. Others have tried to speculate on molecular parameters common to all of the groups. Both approaches are reviewed below.

1. Macrocyclic Musks

One of the first attempts to correlate the structure and odor of macrocyclic musks was carried out by Dyson in 1929.[185] He studied a series of cyclic ketones and the effect of ring size on their odors. He found that the musk odor was present in ketones containing between 13 and 18 carbon atoms, with the most intense odorant being cyclopentadecanone (**73**). He suggested that the musk intensity was related to ring strain. Beets[186] carried out a similar study in 1978. He concluded that the strong musk odor was found in ketones containing 14–16 carbon atoms. An increase in the ring size leads to the introduction of animalic notes and a decrease in the musk intensity until, at a ring size of >20 atoms, the ketones become odorless. Smaller cyclic ketones (7–11 atoms) are camphoraceous in odor.

In the early 1930s Carothers *et al.*[187,188] looked at the effect of replacing the ketone functional group by other carbonyl containing groups (lactone, carbonate, and anhydride). Since examples of musk odorants were found in all four chemical classes they concluded that a C=O group was a necessary feature of the ring for musk odor but that the manner of its linkage was not important. One year later Ruzicka[189] demonstrated that the "required" C=O could in fact be substituted by a ring NH group. A few macrocyclic ethers, sulfides, and pyridines have subsequently been reported to have a musk odor.

When two functional groups are present in the ring, the correlation between odor and structure becomes more complicated.[181,190] Introduction of unsaturation can increase the odor intensity of macrocyclic ketones (dihydrocivetone < civetone) and change the quality of the odor from a flowery musk to an animal musk (Exaltone to dehydroexaltone).[191] Replacement of one of the ring carbon atoms by an oxygen atom generally increases the odor intensity of macrocyclic ketones but decreases the odor of lactones. The position of the oxygen atom relative to the functional group is also important. Both Theimer[192] and Klouwen[193] have studied the odor intensity of a series of oxahexadecanolides. Klouwen concluded that the 6-, 10-, 13-, and 14-oxa compounds are weaker in odor than pentadecanolide (**74**), but that 11-oxahexadecanolide is comparable in both terms of odor strength and quality. For diketones and dilactones, the musk odor tends to be strongest when the functional groups are close to one another. For example, Bauer[194] in his study of 17-membered ring dilactones and 7-oxadilactones found that the oxalate was the most potent in each series. He claimed that although tridecamethylene oxalate (**90**) is less stable under acidic and alkaline conditions than ethylene brassylate (**91**), which is one of the most important commercial macrocyclic musks, it has a more intense odor which lasts for over 3 years on a smelling strip (Figure 44). For the benefit of those readers outside the fragrance industry, a smelling strip is a thin strip of blotting paper which is dipped into the odorant and from which the odor of the material is assessed over time. The odor emitted from the freshly dipped strip is known as the fresh odor and that which is emitted from the strip usually 24 h later as the dry-out or dry-down odor. For single ingredients, a marked difference between these two assessments indicates the presence of trace volatile impurities which are present in the freshly dipped sample but, which after 24 h have completely evaporated. For fragrance compositions this technique enables the perfumer to assess how the odor of a fragrance changes with time, thus mimicking its performance in use on, for example, the skin.

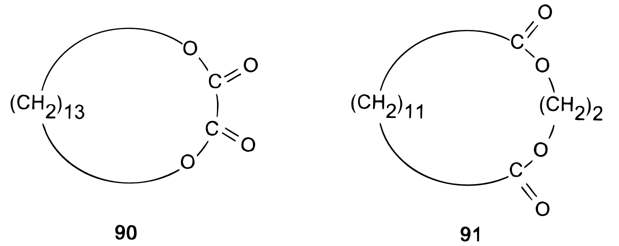


Figure 44. Relative position of the lactone groups and its effect on odor intensity.

When studying structure–odor relationships of these conformationally flexible macrocyclic odorants one has to ask the question "Which conformation is responsible for the perceived musk odor?" In an attempt to answer this question people have drawn comparisons with more rigid musk-smelling compounds such as androst-16-en-3α-ol (**77**)[195,196] and the isochroman (**86**).[3] These comparisons suggest that a stretched conformation, with two long parallel hydrocarbon chains separated by van der Waals radii and bound at each end by bridges containing two or three carbon atoms, may play a more important role in the generation of the musk odor than a quasi-circular one. Bersuker *et al.*[197] also proposed an ellipsoid-like conformation based on their electron-topological rules for musk odor (see section G.4), while Prelog[198] suggested that the carbonyl group was directed toward the inside of the macrocyclic ring **92** since this resulted in increased stabilization by intramolecular bonding and lower reactivity through steric considerations. Determining the preferred conformation in the crystalline state has also proved to be difficult because the crystals tend to show a high degree of disorder. To overcome this, Bernardinelli converted a number of macrocyclic ketones into their corresponding 2,4-dinitrophenylhydrazones (2,4-DNPHs) and used empirical force field calculations to show that the overall influence of the DNPH moiety does not significantly change the ring conformation. The crystal structures of the following ketone derivatives were determined: *cis*-civetone,[199] *trans*-civetone,[200] and muscone.[201] In all three cases, the macrocycle adopted a stretched-type conformation, which was either hexagonal (**93**) or pentagonal (**94**) in shape and in which the functional group was located at the head of the longer axis (Figure 45).

Upon the basis of the assumption that a stretched conformation is indeed important for musk odor,

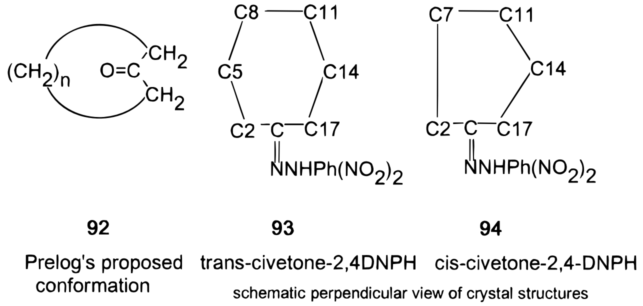
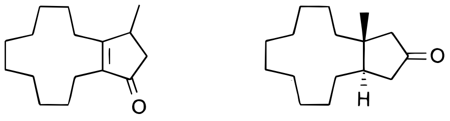


Figure 45. Conformational arrangements of macrocyclic ketones.



95 96

Figure 46. Bicyclic ketones with musk odor.

attempts were made to enforce this desired conformation by introducing bridging bonds. McAndrew and Russell[196] prepared 12 bicyclic analogues of cyclopentadecanone and 3-methylcyclopentadecanone using the cheap and readily available cyclododecanone as their starting material. Two of the products were found to have a distinct musk odor, 15-methylbicyclo[10.3.0]pentadec-1(12)-en-13-one (**95**) and 1-methylbicyclo[10.3.0]pentadecan-14-one (**96**) (Figure 46). In retrospect they concluded that the musk odor of these two materials is somewhat surprising. The suggested reason for this is that the fused nature of the 5- and 12-membered rings gives these bicyclic ketones a wedge-shaped appearance with the rings in separate planes. This is quite different from the flatter disklike shape of the macrocyclic ketones.

2. Nitro Musks

The pioneering work in this field was done by Carpenter.[184] By studying 13 homologues and analogues of musk ambrette (**80**), he observed that all of the derivatives possessing a musklike odor, with the exception of one, had a *tert*-alkyl group ortho to the alkoxy group. However, not all compounds in which this prerequisite is fulfilled are musks. In addition to the "ortho rule" Carpenter also concluded the following:

(1) Replacement of the methoxy group by higher alkoxy groups weakens the odor. The *tert*-butoxy analogues were found to be odorless.

(2) Substitution of higher alkyl groups for the methyl group also decreases the odor intensity except for the case of the ethyl analogue which is stronger than musk ambrette.

(3) Replacement of the methyl group by methoxy results in a strong musk.

In other nitro musks it has been shown that the methyl group can be replaced by bromine, and that one of the nitro groups can be substituted by acetyl, formyl, or *tert*-butyl groups.[202] However, when all of the nitro groups are replaced the odor is destroyed. These findings imply that nitro groups are bifunctional and that, when there is more than one nitro group in the molecule, each of them can act either as a functional group or a profile group.

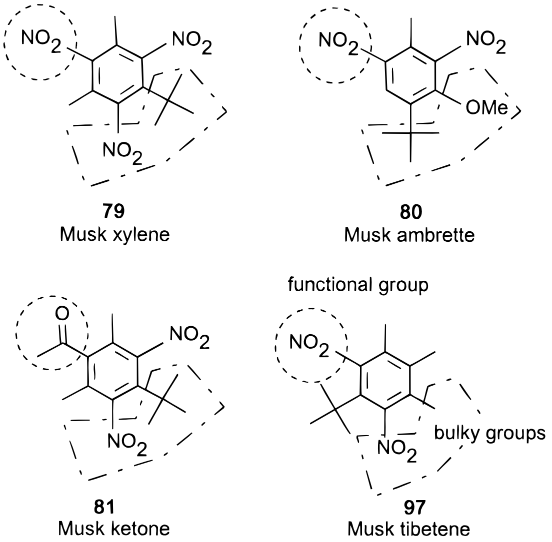


Figure 47. The bifunctional nature of nitro groups.

A similar conclusion was drawn some 30 years later in a comparison of the crystal structures of musk xylene (**79**), musk ambrette (**80**), musk ketone (**81**), and musk tibetene (**97**).[203] These four molecules were shown to fit into one model provided that one of the nitro groups in the latter three cases was acting as a bulky substituent (Figure 47). A number of nitro and acetyl indans were also found to fit the same model.

Jurs and Ham[204] used pattern recognition techniques to study a set of 71 monocyclic benzenoids, 38 of which were musks, and 33 nonmusks. They developed two sets of descriptors which completely separated the compounds into their respective classes. Each set consisted of 13 molecular structure descriptors, 11 of which were common to both sets. These included the following: (1) the "number of heteroatoms" descriptor which reflects the effects of changes in molecular structure on volatility and binding; (2) two geometric descriptors indicating that size and shape are important; (3) substructure molar refractivity descriptors encoding the effects of polarizability; and (4) a connectivity descriptor which reflects steric effects.

The two discriminant models were used to predict the activity of 29 nitrobenzenes. Out of the 19 strong musks, 11 were correctly predicted to be musk, five to be nonmusk, and three were classified differently by the two models. A predictive ability of 58% is not much better than the tossing of a coin.

Molecular descriptors, generated by two alternative methods (autocorrelation and the DARC system), were used by Chastrette[205] for structure activity work. Among the 121 compounds studied, 86% of the musks and 89% of the nonmusks were correctly discriminated. In his study of musk structure−odor relationships, as with his work on camphoraceous and fruit odorants, Chastrette has also evaluated the use of neural networks. One advantage of neural networks over many other statistical techniques is their ability to handle nonlinear data. Chastrette's results from a set of 79 nitrobenzenoids[206] suggest that the relationship between the musk odor and the

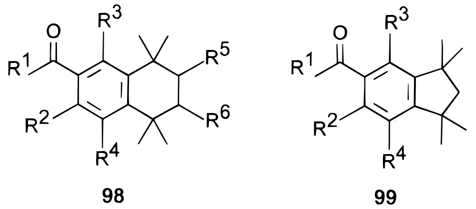


Figure 48. Parent structures used in Chastrette's neural network study.

structural elements of this group of compounds is indeed nonlinear. By comparing the neural network approach with linear discriminant analysis, Chastrette showed that the neural network could correctly classify a higher percentage of the compounds as active or inactive (95% vs 81%). Chastrette[207] has also successfully applied the use of neural networks in the development of a classification model for tetralins and indans with parent structures **98** and **99**, respectively (Figure 48). The relative contribution of each descriptor to the classification was evaluated using three different methods. This ability to interpret the information contained within a neural network is extremely important for compound design. Because of the limited structural variation within the chosen data sets neither of these neural network studies have provided further significant insights into the relationship between chemical structure and musk odor. However, they do demonstrate the potential use of this technique. As with all QSAR methods, the success of this approach will depend upon the correct choice of structural descriptors.

3. Non-nitro Aromatic Benzenoids

The ultimate goal of any SAR study is the design of a novel compound with the desired biological activity. In the field of musk aroma chemicals it was considered in the past, after taking into account performance, stability, and price, that the best chance for a new musk compound lay in the group of non-nitro benzene musks. Today, environmental biodegradability is bringing attention back to macrocyclic musks. Nevertheless, the historical trend resulted in the synthesis of several hundred structurally related benzenoid musks of different odor strength and also a large number of odorless analogues. This unique situation for SAR studies incited Ohloff, Winter, and Fehr to review the past and present trends in the design of new, strong musks belonging to this family.[2] Consequently only a summary of the work they reviewed is given here along with a more detailed account of subsequent or omitted SAR investigations.

The following structural requirements for this group of musks have long been recognized (Figure 49): (1) 14−20 carbon atoms (optimum at C16−C18); (2) an aromatic ring substituted with a functional group (this is usually an acyl group but in certain cases can be replaced by an ether or nitrile function); (3) two quaternary carbon atoms positioned ortho or meta to each other (in the ortho position they are both part of a 5/6-membered ring condensed to the benzene nucleus); (4) sterically unhindered position of the functional group; and (5) closely packed structure.

Rule 5 appears to be very important for musk intensity. The least densely packed structures are represented by the monocyclic meta musks (**100**) which are generally of medium intensity and low tenacity. The bi- and tricyclic meta musks occupy an intermediate position, both in compactness of structure and odor strength whereas the ortho musks (**101**), which are characterized by a densely packed structure, are the strongest and most tenacious.

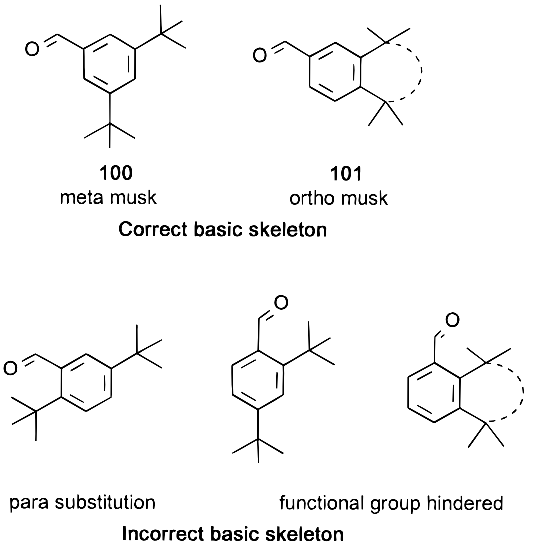


Figure 49. Substitution rules for non-nitro benzenoid musks.

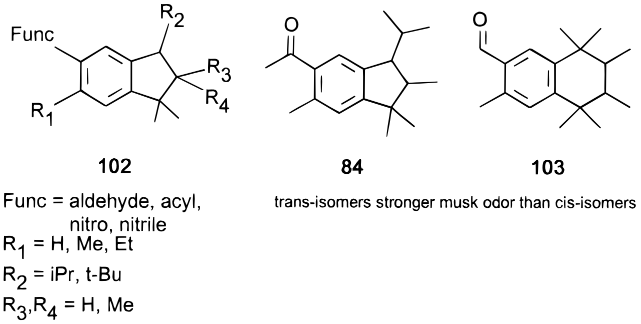


Figure 50. The effect of replacing one quaternary carbon atom with a tertiary carbon atom and the effect of *cis*/*trans* isomerism on musk odor.

With respect to rule 3, Boelens *et al.*[208] investigated whether or not one of the quaternary carbon atoms could be replaced by a tertiary carbon atom substituted with a bulky group. To this end they synthesized a series of indans with the general structure **102** (Figure 50). All of the compounds had some musky odor, but they found that the best was compound **84**, now commercially available as Traseolide. The *trans* and *cis* isomers were prepared separately and found to have different organoleptic properties. The *trans* isomer is a powerful musk while the *cis* isomer has only a moderate musk connotation. A similar relationship is found with the tetralin musk **103** where the *cis* diastereoisomer is clearly weaker than the *trans*.

Schlosser[209] synthesized a range of substituted 1,1,3,3-tetramethyl-1,3-dihydroisobenzofurans (**104**) to investigate the effect of replacing one of the carbon atoms in the saturated carbocycle by an oxygen atom (Figure 51). None of the derivatives had a musk odor. However, the corresponding carbon analogues (**105a−c**) are either odorless or moderately musky.

	R_1	R_2	X	Musk Odor
104a	H	CHO	O	none
104b	H	Ac	O	none
104c	Me	Ac	O	none
104d	Me	$COCH_2CH(Me)_2$	O	none
104e	F	Ac	O	none
105a	Me	CHO	CH_2	moderate (ref 197)
105b	Me	Ac	CH_2	moderate (ref 197)
105c	H	Ac	CH_2	none (ref 197)
105d	Et	Ac	CH_2	strong (ref 197)

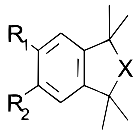
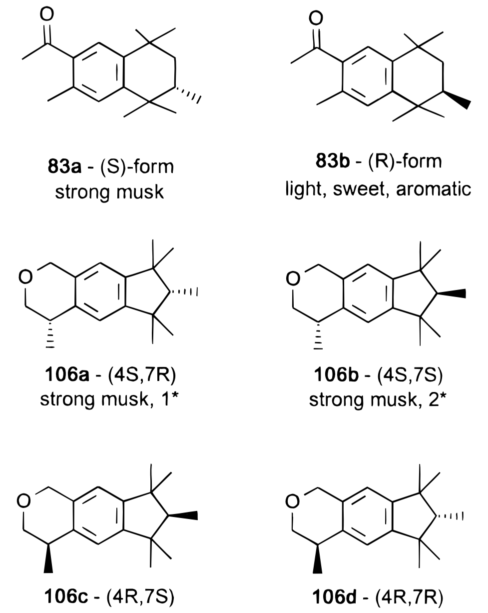


Figure 51. Comparison of odor properties of 1,1,3,3-tetramethyl-1,3-dihydroisobenzofurans and 1,1,3,3-tetramethylindans.


83a - (S)-form
strong musk

83b - (R)-form
light, sweet, aromatic

106a - (4S,7R)
strong musk, 1*

106b - (4S,7S)
strong musk, 2*

106c - (4R,7S)
very weak musk, 250*

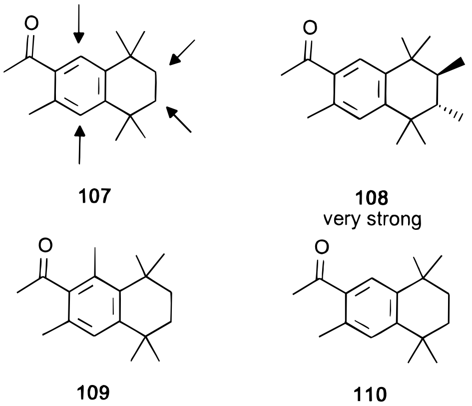
106d - (4R,7R)
very weak musk, 900*

* relative odor threshold values

Figure 52. The effect of chirality on musk odor.

A better comparison would have been one which involved a strongly odoriferous indane musk, such as **105d**.

Musk odor is not only dependent on diastereoisomeric control, but also on enantiomeric control. In the case of Tonalid (**83**), the chirality of the lipophilic part of the molecule has an important effect on the musk odor. The *S* form has a strong musk odor with good fixation properties while the *R* form is light, sweet, and aromatic (Figure 52).[2] For Galaxolide (**106**), on the other hand, it is the chiral center closest to the oxygen atom which is important in determining the odor quality of the molecule. The (4*S*,7*R*)-**106a** and (4*S*,7*S*)-**106b** isomers have a powerful musky odor, whereas (4*R*,7*S*)-**106c** and (4*R*,7*R*)-**106d** isomers have only a very weak odor.[210]


107

108
very strong

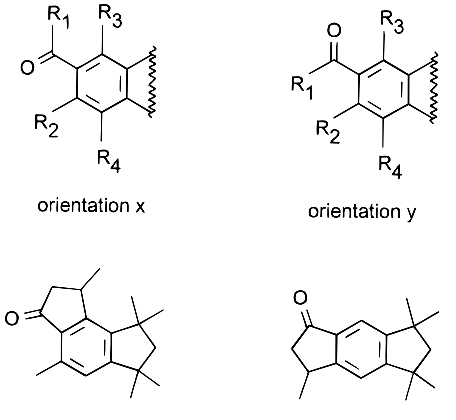
109
strong

110
moderate

Figure 53. The introduction of methyl groups and its effect on musk odor.

In the indan, tetralin, and tricyclic musk series it has been observed that incorporation of methyl groups can lead to stronger musks if the conformational mobility and steric accessibility of the C=O groups are not significantly affected. The observed increase in odor strength was postulated by Ohloff[2] to be related to increased lipophilicity. Fehr *et al.*[211] used this phenomenon in their search for new strong musks. They synthesized a series of molecules based on the musk skeleton (**107**, Figure 53) and introduced methyl groups at the positions indicated. During this study they claim to have discovered the most powerful non-nitro aromatic musk known to date **108**. Despite the generally accepted concept that steric hindrance around a functional group has a negative effect on odor intensity, there are examples where compounds such as **109** possessing two methyl groups α to the carbonyl group are stronger in odor than their corresponding lower homologues **110**. Ohloff[2] believes that in the case of the benzenoid musks there is competition between the benefits of increased lipophilicity and the amount of influence the substituent has on the conformation of the polar group (C=O), the polarity of the molecule and the global shape of the molecule.

There has been some debate over the most favorable conformation of the carbonyl group for musk odor. Ohloff[2] concluded that the carbonyl group should not be prevented from adopting coplanarity with the benzene ring. X-ray analysis[212] has shown that, in many cases, the angle between relatively unhindered carbonyl groups and the benzene ring can be as high as 25°. Although the conformation of a molecule in the crystalline state does not necessarily correspond to the organoleptically active conformation, these results do demonstrate that intermolecular interaction can easily compensate for the loss in conjugation energy. Bersuker[197] claims that the conformation which best satisfies the steric and electronic requirements of his "musk triangle" is not always the one in which the carbonyl and aromatic ring are coplanar and Chastrette[213] postulates that 55° is the optimum angle between the plane of these two groups for hydrogen bonding of the carbonyl group with the receptor (see section G.4). X-ray studies[212] of compounds bearing a methyl group at R_2 and a hydrogen at R_3 show that the acetyl group is invariably facing the methyl group at C2 (orienta-



orientation x

orientation y

111

112

Figure 54. Orientation of the carbonyl group.

tion x, Figure 54), whereas the formyl group can take up either orientation (x or y). Gas-phase molecular modeling experiments produce similar results. Since, in the case of ketones, the musk odor only appears when R_3 is smaller than R_2, Chastrette[207] suggested that for this group of compounds orientation x is more favorable for musk odor. Bersuker[197] considers both carbonyl orientations to be compatible with musk odor. However, the best clues must come from those musk molecules where the orientation is fixed, and in fact, we find that there are examples with the carbonyl group pointed in both directions (**111** and **112**, Figure 54).

Beets[202] suggested that the ease with which the carbonyl group oximates is related to odor intensity. Thus compounds which oximate rapidly are strong musks and those which do not form an oxime are odorless. In fact, the ease of oximation could be a chemical means of measuring the accessibility of the functional group.

Computer-assisted SAR studies have been used to statistically find the most significant molecular descriptors for musk odor. Using the ADAPT software, Jurs *et al.*[214] studied a set of 148 bicyclo- and tricyclobenzenoid compounds of which 67 were musks and 81 nonmusks. They identified a group of 14 molecular descriptors which correctly assigned every compound into its respective category. Some of these descriptors conveyed information about the number of rings, the number of quaternary centers, the distance between the polar heteroatom and both the quaternary centers and the nearest methyl group, and the degree of branching of the substituents attached to the ring. The predictive ability of these descriptors was tested using six musks and nine nonmusks not included in the test set. All of the musks and eight of the nonmusks were correctly classified.

Using a similar technique, the *c*omputer *a*utomated *s*tructure *e*valuation (CASE) methodology, Klopman studied 87 musks and 65 odorless analogues.[215] A QSAR equation relating the strength of musk odor to 23 structural descriptors and $(\log P)^2$ was obtained. Lipophilicity was found to be less important than the structural features. The CASE analysis identified nine structural fragments (odorphores) which were responsible for the odor of musk and seven fragments (odorphobes) encountered exclusively in nonmusk analogues. One of the odorphores closely resembles a structural fragment found in nitro musks, indicating that there may be some overlap in the mechanism of odor perception for these two groups of musks. Klopman's model was tested on 20 chemicals, 10 of which were musks and 10 nonmusks. Two of his predictions were incorrect.

Yoshii[216] found that only three parameters were needed to completely discriminate between her data set of 10 pairs of structurally similar odoriferous and odorless benzenoid musks. Admittedly her data set was considerably smaller than that of Jurs but it did cover various types of benzenoid musks, including monocyclic (one of which was a nitro musk), dicyclic and tricyclic ones. The three parameters were (1) log P, (2) the longest side length of a hexahedron which circumscribed the van der Waals surface of a molecule, and (3) the distance between the oxygen atom of the carbonyl/nitro group and either the nearest and/or the second nearest carbon atom which hinders the approach of the oxygen atom to the receptor site. It was assumed that the receptor site is planar and that, as the molecules approach the receptor plane, the benzene ring and the receptor plane are parallel.

Yoshii[57] subsequently developed a three-dimensional model using only two musk compounds from her original data set, 3,5-di-*tert*-butylacetophenone and 5-acetyl-1,1,2,3,3,6-hexamethylindane. This model consists of two boxes. The first, which circumscribes the whole musk molecule is about 12 × 11 × 6.5 Å and the second, which contains the hydrophobic bulky moiety, about 7.5 × 11 × 6.5 Å. The bottom face of the box represents the hypothesized receptor plane and bears an assumed binding point located 3 Å away from the oxygen atoms of 3,5-di-*tert*-butylacetophenone and 5-acetyl-1,1,2,3,3,6-hexamethylindane. The model was validated using 40 benzenoid compounds (30 musks and 10 odorless). By taking into account conformational flexibility, 37 out of the 40 test compounds were correctly classified. Cyclopentadecanone, one of the macrocyclic musks, was compared with both the structural and the discriminant models and shown not to contradict either. Twenty-three conformations of (*R*)-ethyl citronellyl oxalate[56] were also compared with the 3-D model. On the basis of their closeness of fit to the model, two stable compact conformations were postulated to be the ones responsible for the primary musk odor of this compound. The secondary odor quality, rose, was considered to be due to a more open conformation that bore some resemblance to one conformer of the rose odorant, (*S*)-citronellol.

Minor structural changes, such as the addition or deletion of a single methyl group, can convert an odorless compound into a strong musk. Thus the development a of 3-D model which accounts for these subtle differences surely must require the use of a large number of active and inactive compounds, consideration of multiple conformations and orientations, and a good method of describing shape. One piece of modeling software, which does just this, is a shape-based machine learning tool called Compass. Shape is characterized by measuring the molecule from the outside. Reference points are placed around the molecule and the distance between these and the

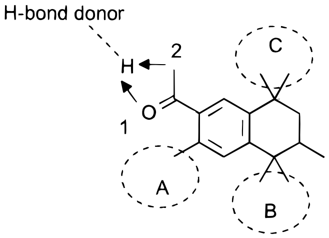


Figure 55. Requirements for musk odor learnt through Compass.

van der Waals surface measured. The molecules are manually aligned in orientations which are sufficiently meaningful for Compass to generate an initial model. The conformations and orientations which produce the best initial model are automatically selected by training a neural network. The shape indices are the input data and the biological activity is the output data. The model is then refined through an adaptive alignment process that automatically generates new molecular poses for each molecule. In the case of Jain's[217] musk study, the initial alignment was based on the benzene ring and the oxygen-containing substituent, and the odor data was of a classified nature (1, musk; 0, nonmusk). Each molecule was conformationally searched and all local minima retained. Thus the final data set contained 6953 conformations of 102 molecules (39 musks, 63 nonmusks). After training and adaptive alignment the resulting model was estimated, from cross-validation experiments, to have a 91% predictive performance. The performance of the model generated from the initial molecular alignment and the single lowest energy conformer of each molecule was significantly lower (75%). The learned model was consistent with other musk activity models. For musk odor, the molecules must have a hydrogen bond acceptor with the appropriate geometry (position 1 or 2) and the appropriate surface shapes in regions A, B, and C (Figure 55).

Jain *et al.*[217] claim that the surface-based shape characterization allows extrapolation of Compass models to novel active chemical classes. To evaluate this they divided the polycyclic benzenoids into four groups: substituted dihydroindanes, indanones, substituted tetrahydronapthalenes, and benzopyrans. They conducted a series of experiments in which all molecules of a given structural class were withheld during training. The resulting model was then used to predict the activity of the omitted molecules. All the molecules in class 1 were correctly predicted, 90% in class 2, 85% in class 3, and 71% in class 4. As one might expect, the predictive performance decreased as the structural diversity increased. It would be interesting to evaluate the predictive ability of the model using nitro musks or macrocyclic musks.

4. SAR Studies Including Different Families of Musks

One of the first studies in this field was carried out by Beets[218] in the mid 1950s. Using molecular models of macrocyclic compounds and benzene derivatives, he suggested that the combination of a sterically accessible functional group and a closely packed profile in a structure with a molecular weight of 220−280 are criteria for the occurrence of musk odor.

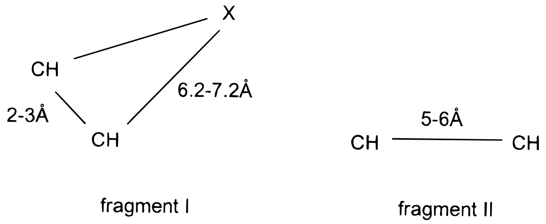


Figure 56. Bersuker's musk activity fragments.

Ten years later Theimer and Davies[192] published their work in this area. They studied more than 50 musk odorants including macrocyclic, isochroman, and *m*- and *o*-benzene musks and found that there was a correlation between the intensity of a compound's musk odor and both its desorption rate from a water surface into air and its molecular dimensions. A good musk was found to have a desorption rate of 0.4−1.7, a molecular cross section of 40−57 Å^2, and a length to breadth ratio of 2.8−3.3.

Pattern recognition was again used by Jurs and co-workers[219] for the analysis of 300 odorants. The data set consisted of 60 musk odorants and 240 nonmusk compounds. The 60 musk compounds included macrocyclic, polynitrobenzenes, steroids, and γ-butyrolactones. The 240 nonmusks were randomly selected from a larger set of data and included camphoraceous, floral, ethereal, mint, pungent, and putrid odorants. Linear discriminants were found which could differentiate between the musk and nonmusk compounds using 13 molecular structure descriptors. Although Jurs admits that the actual meaning of each descriptor is unclear, they do in fact fall into two categories, chemical composition, and geometric shape. The model was tested on nine previously unused musk odorants: all were correctly classified.

In a study of 224 nitro- and non-nitro benzene, indan, and tetralin derivatives, Chastrette[213] suggested that hydrogen bonding was important for the interaction between olfactory receptors and musk odorants. The carbonyl and nitro group were considered to be equivalent and, because of the constraints of H-bonding, the angle between the plane of these groups and the benzene nucleus forced to be 55°. This was confirmed from data on crystals of similar molecules. The *tert*-butyl group was also considered to be important for interaction by dispersion forces.

In 1991 Bersuker and his co-workers[197] used their electron-topological approach to establish the following rules for musk odor.

(1) Two independent structural features are required (Figure 56). The first feature consists of a functional group (CO, NO, CN) whose electronegative atom (X in Figure 56) is situated symmetrically and at a distance of 6.2−7.2 Å with respect to two methyl (or methylene) groups, the distance between the latter being 2.0−3.0 Å. The second fragment includes two other methyl (or methylene) groups separated by a distance of 5.0−6.0 Å.

(2) The features I and II may not be sufficient for musk fragrance activity. The main additional re-

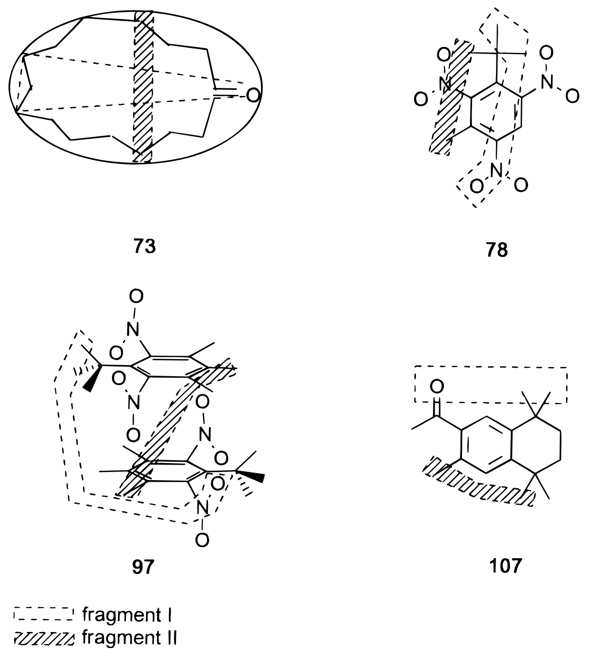


Figure 57. Realization of Bersuker's musk activity fragments I and II in some representative musk compounds.

quirement is that steric accessibility of the two fragments is guaranteed.

They used many examples to illustrate these rules, four of which are shown in Figure 57. In the case of the macrocyclic musks, it was suggested that they can adopt an ellipsoidlike conformation with the larger axis realizing the activity fragment I and the small axis the activity fragment II. The required distances can only be met with macrocycles containing 13−17 members. Any increase or decrease in the number of members may result in a change in the length of the ellipsoid and hence in the reduction of the musk intensity. For a few aromatic compounds it was suggested that the musk odor was associated with dimers. One example is musk tibetene (**97**). In its monomeric form this compound apparently does not contain feature I. However, the corresponding sandwich dimer contains both of the proposed musk activity fragments.

H. Wood

The term wood is used to describe an odor class which includes not only the odor of essential oils derived from various trees such as cedarwood and sandalwood but also some oils derived from leaves (Patchouli oil) and grass (Vetiver oil). Brunke[220] classified woody materials into those with woody-musky, woody-ambergris, earthy-woody, and sandalwood fragrances, and those derived from monoterpenes and sesquiterpenes in his excellent review of woody aroma chemicals. He describes the origin of numerous woody compounds and the effect that simple transformations have on their odor characteristics. From the examples quoted he concludes that the general basic structure for a woody odorant is a rigid bulky hydrocarbon skeleton with a peripheral polar osmophoric group. Typically these compounds are bicyclic or tricyclic with 12−17 carbon atoms possessing an alcohol, carbonyl, or ester functional group.[112] Structural requirements for a number of specific woody aspects are discussed in the following sections.

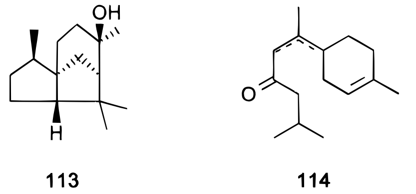
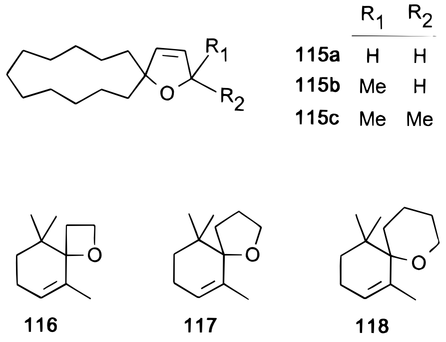


Figure 58. (+)-Cedrol (**113**) and atlantone (**114**).



	R_1	R_2
115a	H	H
115b	Me	H
115c	Me	Me

Figure 59. Structure−woody relationships of spirofurans.

1. Cedarwood

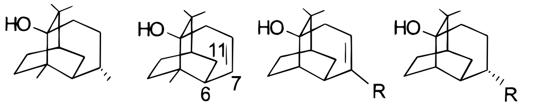
There are two classes of species called cedar: the Chinese and American oils which mainly derive their characteristic "cedar note" from (+)-cedrol (**113**) and Himalayan and Atlas cedars which contain bisabolane derived odorants, such as atlantone (**114**) (Figure 58). Cedrol and atlantone are very different in terms of both their structure and odor and therefore must be treated separately when studying structure−odor relationships.

Cedrol, which is a very rigid molecule, has been used as the standard for comparing the shapes of seven other molecules reported to have an odor of cedarwood or a related woody oriental tobacco note.[221] The similarity in shape was represented by the percentage of the surface of each molecule in a given conformation which coincided with the surface of cedrol. It was found that there was a good fit where eight atoms along the edge of the cedrol molecule, known as the cedrol ridge, were in close proximity to atoms of each of the seven molecules.

In 1992, Weyerstahl[222] discovered that the macrocyclic spiroethers (**115a**−**c**, Figure 59) possess a dominating woody character reminiscent of cedar, while the corresponding saturated compounds still smell woody, but are relatively weak. Further investigations into the structure−activity relationships of spiroethers revealed that the size of the heterocyclic ring has a strong influence on the odor of the theaspirane derivatives (**116**−**118**, Figure 59).[223] The odor intensity rapidly decreases from strong (**116**) to medium (**117**) and weak (**118**), and the quality varies from dominating camphoraceous (**116**) to camphoraceous-herbaceous green (**117**) to floral-woody and fruity (**118**).

2. Patchouli

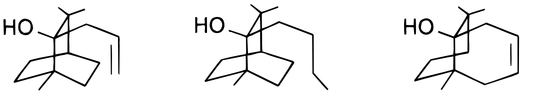
Patchouli oil is obtained by steam distillation of the dried leaves of *Pogostemon cablin* and has an odor which is characteristically described by three key



119 **120** **121** R = H **122** R = Me **123** R = H **124** R = Me

Compound	Wood	Earth	Camphor
119	+++	++	+++
120	+++	+++	+++
121	++++	+++	+
122	++	+++	+
123	+	+++	++++
124	++++	++	+

Figure 60. The effect of the bridgehead-bonded methyl group on patchouli odor.



125 earthy odor, strong camphoraceous by-note

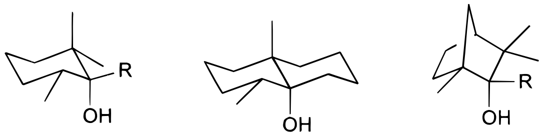
126 intense woody odor slighty camphoraceous

127 intense camphoraceous odor, weak woody by-note

Figure 61. Odor properties of alcohols containing partial bicyclic structures of patchoulol and norpatchoulenol.

odor aspects; woody, earthy, and camphoraceous. The typical patchouli odor is considered to be due to the presence of two sesquiterpene alcohols. The first of these, (−)-patchoulol (**119**), is the main constituent of the oil (30−60%), while the second, (+)-norpatchoulenol[224] (**120**), is a minor component. The chirality of alcohol **119** is important for its olfactory properties; (−)-**119** possesses a strong and typical patchouli scent, while (+)-**119** has a much weaker, nearly indefinable odor.[225] The influence of the bridgehead-bonded methyl group of both alcohols and the olfactory properties of the corresponding unsaturated (**121** and **122**) and saturated derivatives (**123** and **124**) were studied by Spreitzer.[226] The results are summarized in Figure 60 where the key odor descriptors are compared with the naturally occurring terpenes (−)-**119** and (+)-**120**.

Mookherjee[227] successively degraded the tricyclic nucleus to bicyclic and monocyclic partial structures to investigate whether simplification of the structural system could generate molecules with a patchouli-like odor. He found that excessive degradation leads to a loss of the harmonious interaction of the three odor aspects. Similar conclusions were drawn by Weyerstahl[228] during his synthesis of a series of monocyclic partial structures. Weyerstahl and Spreitzer have also investigated moderate degradation to bicyclic partial structures. Spreitzer's[229] approach was to formally cut the C6−C7 bond in patchoulol (**119**) and norpatchoulenol (**120**) and to omit the methylene group of C11 in norpatchoulenol (**120**). The odor properties of the resulting products (**125**−**127**) are shown in Figure 61. Weyerstahl[230,231] found that the odor of bicyclo[2.2.2]octan-2-ones and bicyclo[2.2.2]octan-2-ols shifted from strongly camphoraceous to the more balanced woody, earthy, and camphoraceous character of patchouli depending upon the degree of steric shielding round the functional group. A summary of this work is included in Weyerstahl's review on the relationship between odor and structure.[5]



128 **129** **130**

Figure 62. Comparison of the profiles of 1-alkyl-2,2,6-trimethylcyclohexanols (**128**), geosmin (**129**), and 1-alkylfenchols (**130**).

A similar shift in odor character has been observed for the *cis* and *trans* isomers of 1-alkyl derivatives of 2,2,6-trimethylcyclohexanol (**128**).[232] The *trans* isomers are mainly camphoraceous with a faint earthy note while the *cis* isomers have a strong earthy odor, very similar to that of geosmin (**129**). Pelosi *et al.* proposed that if the preferred conformation for the *cis* isomers is assumed to be a chair cyclohexane system with the hydroxyl group axial, then these derivatives have a very similar profile to that of geosmin (Figure 62). The earthy-smelling 2-methyl- and 2-ethylfenchol derivatives (**130**) also fit this model.

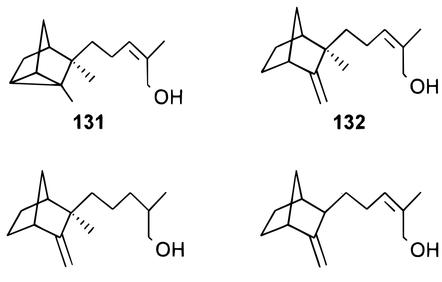
3. Sandalwood

Sandalwood oil comes from the sandalwood tree (*Santalum album*). The most important sandalwood essential oil, with respect to perfumery, is the East Indian oil. It is highly valued for its sweet, warm, spicy, precious-woody fragrance of great tenacity. Its principal constituents, which account for up to 90% of the oil, are α-santalol (**131**) and *β*-santalol (**132**) (Figure 63). These are responsible for the woody character of the oil with *β*-santalol being of greater significance.

The great importance of the "sandalwood" note and the fluctuations in price and availability of East Indian sandalwood oil stimulated the search for synthetic substitutes. The santalols themselves have been synthetic targets in the past and although none of the syntheses were applicable to commercial-scale production, these investigations did provide some insights into the relationship between chemical structure and sandalwood aroma.[233,234]

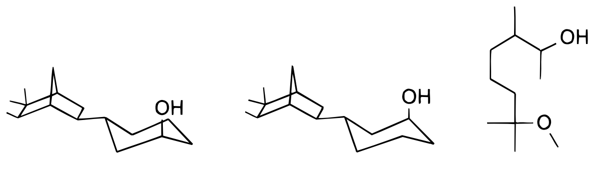
(1) Racemic santalols have odors similar to those of the enantiomerically pure natural compounds.

(2) Dihydro-*β*-santalol (**133**) has a strong sandalwood odor; thus side chain unsaturation appears unimportant. In contrast tetrahydro-*β*-santalol, ob-



131 **132** **133** **134**

Figure 63. Santalols.



135a **135b** **136**

Figure 64. Sandalwood aroma chemicals.

tained by complete saturation, retains only a slight woody-cedar-like fragrance.

(3) Surprisingly, geometry of the side-chain double bond does not have any profound effect on the odor.

(4) The methyl group at C6 has little effect on the odor quality as is shown by 3-desmethyl-β-santalol (**134**).

Two of the early commercial sandalwood aroma chemicals appear to have resulted from chance discoveries. The first is a mixture of isomeric terpenylcyclohexanols, obtained by the condensation of either phenol or guaiacol with camphene and subsequent hydrogenation. The composition of this product was determined by Erman[235] and Demole.[236−238] Rearrangement of the "3-isocamphyl" carbocation at the condensation stage leads to three terpenyl systems. The terpene system required to produce the sandalwood odor is the 2,2,3-*exo*-trimethylnorborn-5-*exo*-yl (*exo*-isocamphanyl) system. During this work, Demole made the significant finding that only the isomers with axial hydroxyl groups possessed sandalwood odors and that the isomers with an axial hydroxyl group in the 3 position of the cyclohexane ring were up to 100 times stronger than the C-2 axial isomers. Thus only two isomers (**135a** and **135b**, Figure 64), present at levels of 5−8% by weight, are predominantly responsible for the sandalwood note of the terpenylcyclohexanol mixture. The second sandalwood aroma chemical which appears to have been discovered by serendipity is Osyrol (**136**, Figure 64).[239,240] This compound is obtained by the epoxidation and addition of methanol to dihydromyrcene, followed by epoxide cleavage. For a more detailed account of the chemistry of sandalwood odorants, including the synthesis and structural elucidation of the santalols, the reader is referred to the reviews of Brunke[233] and Klein.[234]

Naipawer[241] and Brunke[233] used variations of the following rules in their search for new sandalwood aroma chemicals:

(1) The molecule should be a monohydric alcohol.

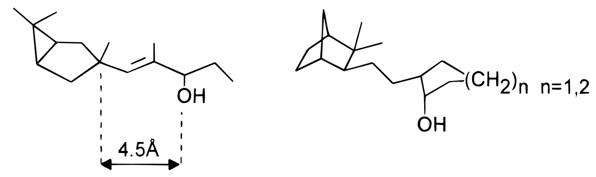
(2) There should be 12−17 carbon atoms.

(3) There should be a highly substituted or quaternary carbon atom at a certain distance (ca. 4 Å) from the oxygen atom of the hydroxyl group.

(4) When the hydroxyl group is part of a side chain there should be a lower alkyl group situated α to the hydroxyl group.

(5) There should be an electron-rich position (a double bond, a cyclopropane ring, or an ether function) near the quaternary center.

These two authors recognized that there were exceptions to this model. They stated that although sandalwood odorants conform to these rules, not all compounds meeting these requirements have a sandalwood odor. Despite this, the above rules are generally considered to have a good predictive value

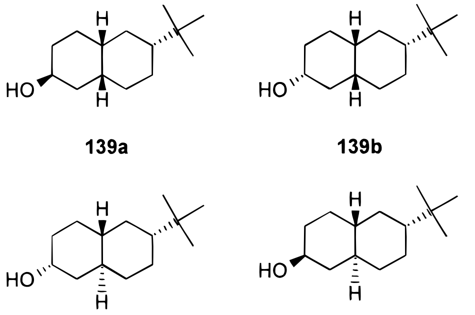


137 **138**

side chain unsaturation crucial for sandalwood odor

Unsaturation has detrimental effect on odor

Figure 65. The effect of side-chain unsaturation on sandalwood odor.



139c **139d**

Figure 66. The four isomers of 8-*tert*-butylbicyclo[4.4.0]decanol.

and have been used by several other workers in the search for new sandalwood aroma chemicals. Sukh Dev[242] during his synthesis of 3,6,6-trimethylbicyclo[3.1.0]hexane-3-carboxaldehyde derivatives found that 1′-(3,6,6-trimethylbicyclo[3.1.0]hex-3-yl)-2′-methylpent-1′-en-3′-ol (**137**, Figure 65), which had an oxygen−quaternary carbon distance of 4.5−5.5 Å, possessed a good sandalwood aroma. Other criteria shown to be important in this class of compounds were substitution at C-4 and the presence of a cyclopropane ring. However, in contrast to the santalols, side-chain unsaturation also appeared to be crucial. Hydrogenation of **137** to the corresponding saturated alcohol resulted in the disappearance of the sandalwood odor; the saturated product was described as having a camphoraceous, green, woody odor of moderate intensity. In a recent investigation into the organoleptic properties of a series of dimethylnorbornane alcohol derivatives it was found that the sandalwood odor was more pronounced in the fully saturated products (**138**, Figure 65).[243] The introduction of a double bond into the aliphatic chain connecting the two cyclic systems had a detrimental effect on the odor, as did the introduction of a methyl group into the 3 position of the cyclohexane part of the norbornane system. Presumably the latter effect is due to increased steric hindrance around the osmophoric hydroxyl group. In agreement with the findings of Demole, it was also concluded that the hydroxyl group should be axial.

Witteveen and van der Weerdt[244] used the steroid, 5α-androst-16-en-3α-ol (**77**), which has an odor reminiscent of sandalwood, as the basis for their research. They synthesized a series of structurally related *tert*-butylbicyclodecanols and found that, out of the isomers **139a**−**d**, only **139c** possessed pronounced sandalwood odor (Figure 66). By comparing the Dreiding and space-filling models of these compounds

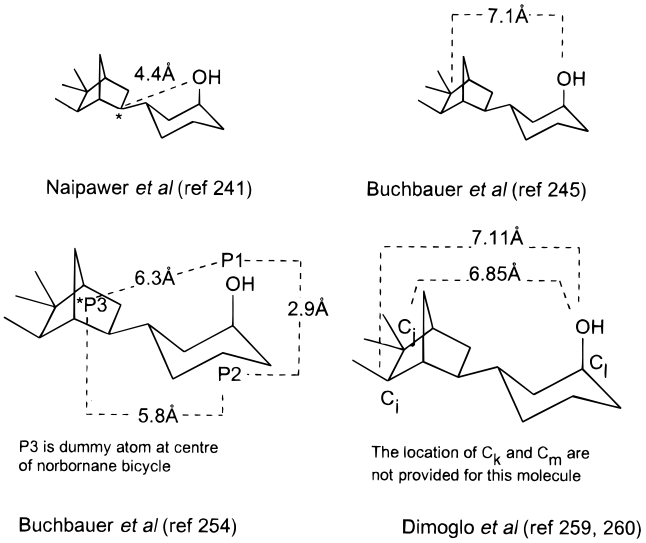


Figure 67. Comparison of sandalwood osmophores.

they suggested that for a sandalwood odor the following molecular criteria should be met:

(1) The shape of the molecule between the hydroxyl group and the bulky tertiary group should be flat.

(2) The hydroxyl group should be axial.

(3) The distance between the hydroxyl group and the quaternary C atom is not indicative of compounds having a sandalwood odor, but might nevertheless be a prerequisite.

The discovery of the above new synthetic sandalwood odorant assisted Buchbauer and his co-workers in the conformational analysis of several sandalwood compounds.[245–253] 8-*tert*-Butylbicyclo[4.4.0]decanol (BBD) is an extremely rigid molecule: only the *tert*-butyl group and the hydroxyl group are free to rotate. Both of these rotations can be neglected because rotation of the symmetrical *tert*-butyl group leads to identical conformations and rotation of the hydroxyl group does not significantly change the shape of the molecule. Thus the active isomer of BBD (**139c**) is represented by one definite conformation and therefore is an excellent standard against which to compare the allowed conformations of other sandalwood odorants. This approach is sometimes referred to as the active analogue approach. Compounds which have been investigated by Buchbauer *et al.* include the two active,[245,246] and four of the inactive isomers of 2,2,3-*exo*-trimethylnorborn-5-*exo*-ylcyclohexanol,[246] β-santalol,[246,247] 3-[(2,2,3-trimethylcyclopent-3-en-1-yl)methyl]cyclohexanol,[246,247] and androstenol.[246] Like Witteveen and van der Weerdt, Buchbauer also concluded that sandalwood odor molecules consist of a more or less flat structure linking a rather exposed polar group on one end to a bulky aliphatic residue on the other. The distance between the hydroxyl group and the bulky group and the shape of the bulky group were also considered to be important. The distances between the hydroxyl group and the quaternary carbon atom in both the active isomer of BBD and the threo isomer of 2,2,3-*exo*-trimethylnorborn-5-*exo*-ylcyclohexan-3β-ol were estimated to be 7.1–7.2 Å[245](Figure 67).

Buchbauer and co-workers went on to refine their sandalwood model by comparing the molecular shapes of a few selected sandalwood odorants with the shapes of structurally similar, but nevertheless inactive, compounds. Molecular shape comparison was based on either overlapping volumes and/or the comparison of molecular surfaces. In all cases, the compounds under investigation were subjected to a full conformational analysis using 8-*tert*-butylbicyclo-[4.4.0]decanol (BBD) as the standard prior to any molecular comparison. The molecular shape comparison approach led to the following conclusions regarding the structural requirements for sandalwood odor:

(1) There is a correlation between overlapping volume and odor.[248]

(2) The molecular surface of structurally similar but inactive compounds deviate considerably from the calculated mean surface of sandalwood odorants.[249,250]

(3) The surface region around the hydroxyl group and a part of the hydrophobic bulky group seem to be very important in determining the sandalwood odor of a molecule. Other parts of the molecular surface can tolerate greater surface variations.[251–253]

(4) Although androstenol is much larger than other sandalwood odor molecules, 70% of its surface coincides with the “sandalwood” mean surface.[252] This may explain why androstenol is perceived by some human subjects as sandalwood. It is also described by others as being musky or urinous.

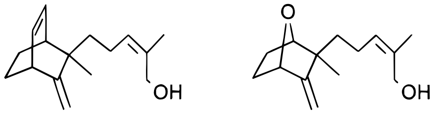
Interestingly, in one of Buchbauer's[254] more recent conformational analyses, he found that BBD was too rigid to be the conformational standard since not all of the sandalwood molecules could be fitted to the BBD conformation. One explanation is that although 8-*tert*-butylbicyclo[4.4.0]decanol (BBD) is ideal for conformational comparisons it is not the most active sandalwood material and thus not necessarily the best standard. Buchbauer, using the more flexible 3-(2,2,2-trimethylcyclopent-3-enyl)cyclohexan-1-ol as the reference compound, identified two very similar orientations of three key structural groups (or osmophoric points). The three osmophoric points were the hydroxyl group (P1), a carbon atom in close proximity to the hydroxyl group (P2) and the center of the bulky group (P3). The distances between P1 and P2, P1 and P3, and P2 and P3 were 2.9–3.0, 6.2–6.4, and 5.6–6.0 Å, respectively. These osmophoric points for compound **135b** are shown in Figure 67. The sandalwood osmophore was subsequently tested using some structurally similar but odorless compounds. Although in some cases conformations were found which fitted the osmophoric distance constraints, they showed significant deviations from the mean sandalwood molecular surface. This confirms the need to combine distance criteria and molecular shape in the development of three-dimensional SARs.

For this work Buchbauer used the systematic SEARCH function available within the Tripos SYBYL molecular modeling package. The main drawback with this module is that the osmophoric points have to be defined by the chemist or molecular modeler prior to the conformational search. This introduces human bias into the model and does not allow one to look for the unexpected. Buchbauer chose his osmophoric points on the basis of previous sandalwood SAR observations. However, there are a range of software packages which are capable of automatically identifying biophores, such as DISCO from Tripos, APEX from Biosym, and CATALYST from Molecular Simulations. These have been primarily developed for drug discovery and are thus designed to handle highly functionalized molecules. Fragrance compounds, on the other hand, tend to have only one or two functional groups. To date, only one of these packages (CATALYST) has been used in the study of structure-odor relationships[19] (see section IV.A).

Wolschann *et al.*[255] have applied the molecular shape comparison technique to the stereoisomers of β-santalol (**132**) and 8-*tert*-butylbicyclo[4.4.0]decanol (**139**). The stereoisomer of natural (−)-β-santalol has recently been synthesized and found to be odorless.[256] Odor differences for the (+) and (−) isomers of 8-*tert*-butylbicyclo[4.4.0]decanol have also been reported with the (+) isomer described as having a sandalwood odor and the (−) isomer described as odorless.[257] Wolschann concluded, from his molecular-shape comparison, that there were no significant differences between the total molecular surfaces of the odoriferous and odorless compounds. However, large differences are apparent if the surfaces of the hydrophobic part of the molecules are compared (i.e. the bulky group). Surprisingly, there has been relatively little information published concerning the dependence of sandalwood odor on the absolute configuration of chiral substrates. Apart from the aforementioned three papers the only other reference to the effect of chirality on sandalwood odor is a statement made by Ohloff[2] in his review on structure−odor relationships. He claims that "during work carried out at Firmenich, significant differences in odoriferous activity between enantiomers in the series of campholenic aldehyde derivatives have been noticed".

Chastrette[258] in 1990 studied a set of 139 compounds, 51 of which were active and 82 inactive, in the search for an interaction model based on the concept of a santalophore superpattern. Two santalophore patterns were proposed, pattern I and pattern II. The quaternary carbon−hydroxyl oxygen distance was found to be 7.1 Å in pattern I and 6.5 Å in pattern II. Since the difference between the distances was not very significant it was concluded that molecules possessing patterns I and II probably interact with different parts of the same receptor. Therefore the receptor must be slightly larger than the two patterns, and thus, the concept of a superpattern was introduced. In attempting to further describe the geometric characteristics of the superpattern, Chastrette found that a complete discrimination between active and inactive molecules is obtained when the distances and dihedral angles between the hydroxyl oxygen atom and the methyl groups of the bulky residue are used.

Recently, Dimoglo *et al.*[259,260] used the electron-topological method to investigate the relationship between sandalwood odor and the chemical structure of a number of alcohols. The data set consisted of 30 active compounds and 21 inactive compounds. For each compound, electron-topological matrices of contiguity (ETMC) were generated and subsequently compared with the ETMC of a standard compound (for a more detailed account of ETMCs see section IV.A). This led to the identification of an activity fragment which was present in all of the active compounds but absent in the inactive ones. The activity fragment consisted of two distinct groups of atoms. The first contains two adjacent carbon atoms, C_i and C_j, which are quaternary or tertiary in nature and which possess a small positive charge. The second group contains the hydroxyl group and three neighboring carbon atoms (C_k, C_l, C_m), where C_k is also quaternary or tertiary. The distances between the hydroxyl group and both C_i and C_j were estimated to be 6.4−6.8 and 7.4−7.8 Å respectively. The first activity feature for compound **135b** is shown in Figure 67. The atoms which form the activity fragments were also shown, by analysis of the HOMO and LUMO wave functions, to be centers of high reactivity. On the basis of these observations Dimoglo suggested that C_i and C_j form an electron donor center and that C_k, C_l, and the hydroxyl group an electron acceptor center.



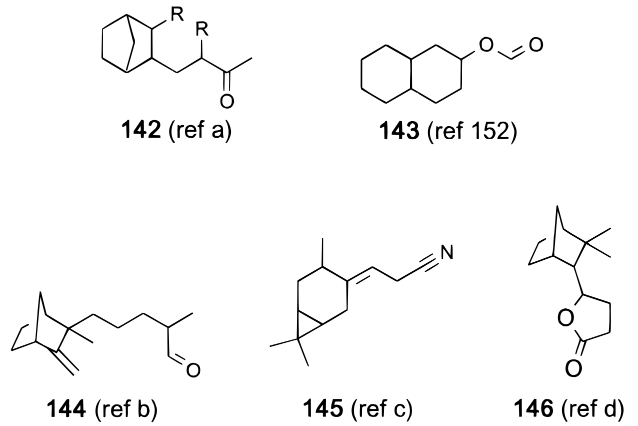
140 **141**

Figure 68. Buchbauer's novel santalols.

In summary, there have been over 20 publications on the relationship between chemical structure and sandalwood odor and in each case the basic conclusions have been the same. Compounds which smell of sandalwood tend to be flat with a polar hydroxyl group located at one end and a bulky residue at the other end. The hydroxyl group is orientated approximately perpendicular to the plane of the molecule and separated from the bulky group by a certain distance. The distance varies depending upon which atom (or center) the author has chosen to be the measurement point in the bulky residue. This is illustrated in Figure 67 for four different SAR publications using compound **135b** as an example.

Buchbauer has used his sandalwood models to design novel santalol analogues, for example (*Z*)-dehydrohomo-β-santalol[261] (**140**) and (*Z*)-7-oxa-β-santalol[262] (**141**) (Figure 68). Although both of these materials fulfill the proposed steric requirements only **140** has the predicted sandalwood odor. Replacement of the methylene bridge in β-santalol (**132**) by an oxygen atom to give **141** causes destruction of the odor. The same effect is observed in homocamphenilone (**35**, Figure 20)[123] (see section IV.C). This illustrates the need to combine osmophore and shape models with QSARs which take into account electronic properties such as electrostatic potential and transport properties such as log P and volatility.

It should also be pointed out that all of the sandalwood SAR studies have focused on one chemical class, namely alcohols. Although the majority of known sandalwood compounds do belong to this chemical family, there are a few examples of compounds from other chemical classes which have been described as having an odor reminiscent of sandalwood (**142**−**146**, Figure 69). Since these unique compounds might contain vital clues regarding the structural requirements for sandalwood odor they should be the focus for future SAR and molecular modeling studies. However, because their prepara-



142 (ref a) **143** (ref 152)

144 (ref b) **145** (ref c) **146** (ref d)

Figure 69. Compounds from other structural classes reported to have a sandalwood odor. References: (a) Schleppnik, A. A. German Patent DE 2200090, 1972; *Chem. Abstr.* **1972**, *77*, 126149p. (b) Pieper, K. M.; Gibson, T. W. U.S. Patent 3673256, 1972; *Chem. Abstr.* **1972**, *77*, 113904. (c) Kettenes, D. K.; Lenselink, W. German Patent DE2812288, 1978; *Chem. Abstr.* **1978**, *90*, 39073. (d) Buchbauer, G.; Hell, I.; Schindler, K. *Monatsch. Chem.* **1981**, *112*, 841.

tion might lead to the presence of trace alcohol impurities it is recommended that these compounds are subjected to rigorous olfactory purity testing. The fruit of such research might be the discovery of a new family of sandalwood odorants!

One intriguing observation about sandalwood is that oxidation of a sandalwood alcohol often produces a urinous ketone. This relationship in chemical structure between sandalwood and urinous odors is reviewed by Brunke and Klein.[216] The link is also apparent among odoriferous steroids with, for example, 5α-androst-16-en-3-one having a strong urinous odor and 5α-androst-16-en-3α-ol (**77**) a sandalwood and musklike odor. The relationship between the odoriferous properties of steroids (sandalwood-musk, urine, or ambergris) and their chemical structure has recently been reviewed by Ohloff.[4]

V. Concluding Remarks

By providing a comprehensive review of the work which has been carried out in relating structure with odor, this article contains guidelines which will be useful for the fragrance chemist in his search for new aroma chemicals. The potential for SAR in fragrance design is exemplified by the studies where structure–odor relationships and/or molecular modeling have led to the discovery of new fragrance ingredients.[19,130,134,137,205,208,259]

It is noticeable that whatever odor "rules" are deduced, there are always exceptions. The nonodoriferous exceptions are probably explained by steric hindrance to a receptor fit or lack of volatility, but compounds which have anomalous odor characteristics or intensities are not as easy to explain. Trying to understand why these compounds do not fit the models may provide useful clues about the mechanism of olfaction. Indeed, as progress in the biological sciences leads to an increased understanding of the mechanism of olfaction and as more sophisticated SAR tools become developed, the search for correlations between structure and odor should become easier. This challenge, coupled with the potential predictive ability of this approach, will entice chemists and molecular modelers to continue research in this area. Significant advances in olfactory research will probably only be made by the close interaction of scientists from different disciplines: organic chemists, biochemists, SAR workers, and molecular modelers.

VI. Acknowledgments

With pleasure and gratitude I thank all of my colleagues at Quest International and Dr. John Mitchell, my academic Ph.D. supervisor, for their support and encouragement. I am also grateful to Richard Butcher for his help in obtaining relevant literature and Dr. Michael Tute of Pfizer, Sandwich, for his comments on the first draft of this review. A special thanks goes to Dr. Charles Sell for helpful discussions and for reading the manuscript and offering useful comments.

VII. References

(1) Somogyi, P. L. *Chem. Ind.* **1996**, 170.
(2) Ohloff, G.; Winter, B.; Fehr, C. In *Perfumes - Art, Science, Technology*; Müller, P. M., Lamparsky, D., Eds.; Elsevier Applied Science: New York, 1991; pp 287–330.
(3) Beets, M. G. J. In *Structure-activity Relationships in Human Chemoreception*; Applied Science Publishers Ltd.: London, 1978.
(4) Ohloff, G. In *Scent and Fragrances - The Fascination of Odors and their Chemical Perspectives*; Springer-Verlag: Berlin, Germany, 1994; pp 9–56.
(5) Weyerstahl, P. *J. Prakt. Chem.* **1994**, *336* (2), 95.
(6) Amoore, J. E. *Perfum. Essent. Oil Rec.* **1952**, *43*, 321.
(7) Amoore, J. E. *Proc. Sci. Sect. Toilet Goods Assoc.* **1962**, *37*, 13.
(8) Guillot, M. *Compt. Rend. Acad. Sci.* **1948**, *26*, 143.
(9) Dyson, G. M. *Perfum. Essent. Oil Rec.* **1937**, *28*, 13.
(10) Wright, R. H. *J. Appl. Chem.* **1954**, *4*, 611.
(11) Laffort, P. In *Odors and Deodorization in the Environment*; Martin, G., Laffort, P., Eds.; VCH Publishers: New York, 1994; pp 143–183.
(12) Turin, L. *Chem. Senses* **1996**, in press (Horizon BBC, A Code in the Nose, transmission date Nov 27, 1995).
(13) Morrison, E. E.; Moran, D. T. In *Handbook of Olfaction and Gustation*; Doty, R. L., Ed.; Marcel Dekker, Inc.: New York, 1995; pp 75–101.
(14) Breer, H. In *The Molecular Basis of Smell and Transduction*; Ciba Foundation Symposium 179; Wiley: Chichester, 1993; pp 97–114.
(15) Dionne, V. E.; Dubin, A. E. *J. Exp. Biol.* **1994**, *194*, 1.
(16) Buck, L.; Axel, R. *Cell* **1991**, *65*, 175.
(17) Raming, K.; Kreiger, J.; Strotmann, J.; Boekhoff, I.; Kubik, S.; Baumstark, C.; Breer, H. *Nature* **1993**, *361*, 353.
(18) Singer, M. S.; Shepherd, G. M. *NeuroReport* **1994**, *5*, 1297.
(19) Bajgrowicz, J. A.; Broger, C. In *Flavors, Fragrances and Essential Oils*; Proceedings of the 13th International Congress of Flavors, Fragrances and Essential Oils; Istanbul, Turkey, 15–19 October 1995; Başer, K. H. C., Ed.; AREP Publ.: Istanbul, Turkey, 1995; Vol. 3, pp 1–15.
(20) Ressler, K. J.; Sullivan, S. L.; Buck, L. B. *Cell* **1993**, *73*, 597.
(21) Vassar, R.; Ngai, J.; Axel, R. *Cell* **1993**, *74*, 309.
(22) Strotmann, J.; Wanner, I.; Helfrich, T.; Beck, A.; Meinken, C.; Kubick, S.; Breer, H. *Cell Tissue Res.* **1994**, *276*, 429.
(23) Strotmann, J.; Wanner, I.; Helfrich, T.; Beck, A.; Breer, H. *Cell Tissue Res.* **1994**, *278*, 11.
(24) Ressler, K. J.; Sullivan, S. L.; Buck, L. B. *Cell* **1994**, *79*, 1245.
(25) Strotmann, J.; Beck, A.; Kubick, S.; Breer, H. *J. Comp. Physiol. A* **1995**, *177*, 659.
(26) Math, F. *C. R. Seances Soc. Biol. Ses Fil.* **1993**, *187* (5), 633.
(27) Axel, R. *Sci. Am.* **1995**, October, 130.
(28) Pelosi, P. *Crit. Rev. Biochem. Mol. Biol.* **1994**, *29* (3), 199.
(29) Breer, H.; Raming, K.; Krieger, J. *Biochim. Biophys. Acta* **1994**, *1224*, 277.
(30) Ronnett, G. V. In *Handbook of Olfaction and Gustation*; Doty, R. L., Ed.; Marcel Dekker, Inc.: New York, 1995; pp 127–145.
(31) Prah, J. D.; Sears, S. B.; Walker, J. C. In *Handbook of Olfaction and Gustation*; Doty, R. L., Ed.; Marcel Dekker, Inc.: New York, 1995; pp 227–255.
(32) Neuner-Jehle, N.; Etzweiler, F. In *Perfumes - Art, Science, Technology;* Müller, P. M., Lamparsky, D., Eds.; Elsevier Applied Science: New York, 1991; pp 153–212.

(33) Moy, L.; Tan, T.; Gardner, J. W. *Perfum. Flavor.* **1994**, *19* (4), 11.

(34) Wünsche, L. F.; Vuilleumier, C.; Keller, U.; Byfield, M. P.; May, I. P.; Kearney, M. J. In *Flavors, Fragrances and Essential Oils*; Proceedings of the 13th International Congress of Flavors, Fragrances and Essential Oils, Istanbul, Turkey, 15−19 October 1995; Başer, K. H. C., Ed.; AREP Publ.: Istanbul, Turkey, 1995; Vol. 3, pp 295−313.

(35) Osterhammel, P.; Terkildsen, K.; Zilstorff, K. *J. Laryngol.* **1969**, *83*, 731.

(36) Kobal, G. *Pain* **1985**, *22*, 151.

(37) Cometto-Muniz, J. E.; Cain, W. S. *Chem. Senses* **1984**, *8*, 315.

(38) Hughes, J. R.; Hendrix, D. E.; Wetzel, N. In *Theories of Odor and Odor Measurement*; Tanyolac, N. N., Ed.; Unwin Bros: Old Woking, UK, 1968; pp 87−114.

(39) Moulton, D. G. In *Odor Quality and Chemical Structure*; Moskowitz, H. R., Warren, C. B., Eds.; American Chemical Society: Washington, DC, 1981; pp 211−230.

(40) Freeman, W.; Schneider, W. *Psychophysiology* **1982**, *19*, 44.

(41) Behan, J. M.; Richardson, A. In *Flavors, Fragrances and Essential Oils*; Proceedings of the 13th International Congress of Flavors, Fragrances and Essential Oils, Istanbul, Turkey, 15−19 October 1995; Başer, K. H. C., Ed.; AREP Publ.: Istanbul, Turkey, 1995; Vol. 3, pp 328−335.

(42) Huttunen, J.; Kobal, G.; Kaukoranta, E.; Hari, P. *Electroencephalogr. Clin. Neurophysiol.* **1986**, *64*, 347.

(43) Kettermann, B.; Stefan, H.; Kobal, G. *Chem. Senses* **1995**, *20*, 163.

(44) Kobal, G.; Kettermann, B.; Stefan, H. *Chem. Senses* **1995**, *20*, 164.

(45) Lorig, T. S. *Prog. Neurobiol.* **1989**, *33*, 387.

(46) Cain, W. S. *Chem. Senses* **1982**, *7*, 129.

(47) Jaubert, J. N.; Tapiero, C.; Dore, J. C. *Perfum. Flavor.* **1995**, *20* (3), 1.

(48) Curtis, T.; Williams, D. G. In *Introductory to Perfumery*; Ellis Horwood Limited: Hemel Hempstead, UK, 1994; pp 46−48.

(49) ISO 5496:1992, *Sensory analysis - Methodology - Initiation and training of assessors in the detection and recognition of odors.*

(50) Friedman, L.; Miller, J. G. *Science* **1971**, *172*, 1044.

(51) Boelens, M. H. *Perfum. Flavor.* **1993**, *18* (6), 1.

(52) Chastrette, M.; Rognon, C.; Sauvegrain, P.; Amouroux, R. *Chem. Senses* **1992**, *17*, 555.

(53) Koppenhoefer, B.; Behnisch, R.; Epperlein, U.; Holzschuh, H. *Perfum. Flavor.* **1994**, *19* (5), 1.

(54) Mosandl, A. *J. Chromatogr.* **1992**, *624*, 267.

(55) Mosandl, A. *Food Rev. Int.* **1988**, *4* (1), 1.

(56) Yoshii, F.; Hirono, S.; Moriguchi, I. *Quant. Struct.-Act. Relat.* **1994**, *13*, 144.

(57) Yoshii, F.; Hirono, S.; Liu, Q.; Moriguchi, I. *Chem. Senses* **1992**, *17*, 573.

(58) Harper, R.; Bate Smith, E. C.; Land, D. G. In *Odor Description and Odor Classification*; J., & A. Churchill Ltd: London, UK, 1968.

(59) Boelens, H.; Haring, H. G.; de Rijke, D.; Punter, P. H. Personal Communication, Naarden Int., The Netherlands; 1981.

(60) Abe, H.; Kanay, S.; Komokai, T.; Takahashi, Y.; Sasaki, S. *Anal. Chim. Acta* **1990**, *239*, 73.

(61) Polak, E. *Chem. Ind.* **1983**, 30.

(62) Schiffman, S. S. *Science* **1974**, *185*, 112.

(63) Amoore, J. E. *Nature* **1971**, *233*, 270.

(64) Kier, L. B.; Di Paolo, T.; Hall, L. H. *J. Theor. Biol.* **1977**, *67*, 585.

(65) Dearden, J. C. *Food Quality and Preference* **1994**, *5*, 81.

(66) Boelens, H. In *Structure-activity Relationships in Chemoreception*; Benz, G., Ed.; Information Retrieval Ltd: London, 1976; pp 197−209.

(67) Boelens, H.; Haring, H. G.; Takken, H. J. *Chem. Ind.* **1983**, *1*, 26.

(68) Acree, T. E.; Barnard, J. In *Trends in Flavor Research*; Maarse, H., van der Heij, D. G., Ed.; Elsevier: Amsterdam, 1994; pp 211−220.

(69) Grosch, W. *Trends Food Sci. Technol.* **1993**, *4*, 68.

(70) Cometto-Muñiz, J. E.; Cain, W. S. *Physiol. Behav.* **1990**, *48*, 719.

(71) Cometto-Muñiz, J. E.; Cain, W. S. *Pharmacol. Biochem. Behav.* **1991**, *39*, 983.

(72) Boelens, M. H.; Boelens, H.; van Gemert L. J. *Perfum. Flavor.* **1995**, *20* (1), 1.

(73) Köster, E. P. In *Odors and Deodorization in the Environment*; Martin, G., Laffort, P., Eds.; VCH Publishers: New York, 1994; pp 29−65.

(74) Stevens, S. S. *Psychol. Rev.* **1936**, *43*, 405.

(75) Demole, E.; Enggist, P.; Ohloff, G. *Helv. Chim. Acta* **1982**, *65*, 1786.

(76) Belz, R.; Maarse, H.; van Straten, S.; de Grunt, F. E.; Ruygrok, C. T. M.; Zoeteman, B. C. J. In *Compilation of Odor Threshold Values in Air and Water*; van Gemert, L. J., Nettenbreijer, A. H., Eds.; National Institute for Water Supply and Central Institute for Nutrition and Food Research: Netherlands, 1977.

(77) Christoph, N.; Drawert, F. In *Topics in Flavor Research*; Berger, R. G., Nitz, S., Schreier, P., Eds.; Eichhorn, H.: Marzling-Hangenham, Fed. Rep. Ger., 1985; pp 59−77.

(78) Jurs, P. C.; Edwards, P. A. *Chem. Senses* **1989**, *14*, 281.

(79) Egolf, L. M.; Jurs, P. C. *Anal. Chem.* **1993**, *65*, 3119.

(80) Edwards, P. A.; Anker, L. S.; Jurs, P. C. *Chem. Senses* **1991**, *16*, 447.

(81) Ruzicka, L.; Seidel, C. F. *Helv. Chim. Acta* **1950**, *33*, 1285.

(82) Collin-Asselinuae, C.; Ledener, E.; Mercier, D.; Polonsky, J. *Bull. Soc. Chim. Fr.* **1950**, *17*, 720.

(83) Stoll, M.; Hinder, M. *Helv. Chim. Acta* **1950**, *33*, 1251; **1950**, *33*, 1308; **1953**, *36*, 1995.

(84) Mookherjee, B. D.; Patel, R. R. In *Proceedings of 7th Int. Congr. Essent. Oils*; Tokyo, Oct 7−11, 1977; Japan Flavor Fragrance Manufactures' Assoc.: Tokyo, Japan, 1979; pp 479−482.

(85) Ohloff, G. In *Fragrance Chemistry - The Science of the Sense of Smell*; Theimer E. T., Ed.; Academic Press: New York, 1982; pp 535−573.

(86) Cambie, R. C. *Chem. N.Z.* **1987**, 31.

(87) Ohloff, G. In *Gustation and Olfaction*; Ohloff, G., Thomas, A. F., Eds.; Academic Press: London, New York, 1971; pp 178−183.

(88) Dey, A. K.; Wolf, H. R. *Helv. Chim. Acta* **1978**, *61*, 1004.

(89) Bruns, K. In *Henkel-Referate 25th/Int. Ed.*; Zeidler, U., Ed.; Henkel KGaA: Duesseldorf, Germany, 1989; pp 118−126.

(90) Cambie, R. C.; Hayward, R. C.; Palmer, B. D.; Robertson, J. D.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1982**, *35*, 1699.

(91) Winter, B. In *QSAR: Quantitative Structure-Activity Relationships in Drug Design;* Fauchère, J. L., Ed.; Alan R. Liss: New York, 1989; pp 401−405.

(92) Winter, B. *Helv. Chim. Acta* **1989**, *72*, 1278.

(93) Winter, B. *Pure Appl. Chem.* **1990**, *62* (7), 1377.

(94) Vlad, P. F.; Morary, A. F.; Koltsa, M. N. Russian Patent SU 1169971, 1985; *Chem. Abstr.* **1986**, *104*, 95284.

(95) Bersuker, I. B.; Dimoglo, A. S.; Gorbachov M. Yu.; Koltsa, M. N.; Vlad, P. F. *New J. Chem.* **1985**, *9* (3), 211.

(96) Bersuker, I. B.; Dimoglo, A. S.; Gorbachov M. Yu.; Koltsa, M. N.; Vlad, P. F. In *QSAR in Drug Design and Toxicology*; Hadži, D., Jerman-Blažič, B., Eds.; Elsevier Science Publishers B. V.: Amsterdam, 1987; pp 340−342.

(97) Shvets, N.; Dimoglo, A.; Güzel, Y.; Saripinar, E.; Patat, Ş.; Yildirim, İ. In *Flavors, Fragrances and Essential Oils*; Proceedings of the 13th International Congress of Flavors, Fragrances and Essential Oils, Istanbul, Turkey, 15−19 October 1995; Başer, K. H. C., Ed.; AREP Publ.: Istanbul, Turkey, 1995; Vol 3, pp 16−28.

(98) Dimoglo, A. S.; Vlad, P. F.; Shvets, N. M.; Coltsa, M. N.; Güzel, Y.; Saraçoçlu, M.; Saripinar, E.; Patat, Ş. *New J. Chem.* **1995**, *19*, 1.

(99) Bersuker, I. B.; Dimoglo, A. S. In *Reviews in Computational Chemistry*; Lipkowitz, K., Boyd, D., Eds.; VCH Publishers: New York, 1991; pp 423−460.

(100) Burgen, A. S. V.; Roberts, G. C. K.; Feeny, J. *Nature* **1975**, *253*, 753.

(101) Newman, C. P.; Rossiter, K. J.; Sell, C. S. European Patent 0276998, 1988; *Chem. Abstr.* **1989**, *110*, 13401.

(102) Sell, C. S. *Chem. Ind.* **1990**, *16*, 516.

(103) Bociek, S. Personal communication, Quest International, Ashford, Kent, UK; Brown, C.; Smith, D., University of Kent, Canterbury, Kent, UK; 1989.

(104) Watkins, D. Personal communication, Oxford University, Oxford, UK; 1989.

(105) Guenther, E. In *The Essential Oils*; D. Van Nostrand Company Inc.: Toronto, 1952; Vol 5.

(106) Lindner, P.; Märtensson, O. *Int. J. Quantum Chem.* **1972**, *6*, 363.

(107) Klouwen, M. H.; Ruys, A. H. *Parfum. Cosmet. Savors* **1963**, *6*, 6.

(108) Randic, M. *J. Am. Chem. Soc.* **1975**, *97*, 6609.

(109) Kier, L. B.; Hall, L. H. In *Molecular Connectivity in Chemistry and Drug Research*; de Stevens, G., Ed.; Academic Press: New York, 1976.

(110) Kier, L. B. *Quant. Struct.-Act. Relat.* **1985**, *4*, 109.

(111) Zakarya, D.; Yahiaoui, M.; Fkih-Tetouani, A. *J. Phys. Org. Chem.* **1993**, *6*, 627.

(112) Boelens, H. *Cosmet. Perfum.* **1974**, *89*, 1.

(113) Buchbauer, G.; Kalchhauser, H.; Wolschann, P.; Yahiaoui, M.; Zakarya, D. *Monatsh. Chem.* **1993**, *125*, 1091.

(114) Wright, R. H. *Nature* **1969**, *222*, 290.

(115) Klouwen, M. H. *Perfum. Essent. Oil Rec. Jubilee* **1959**, 27.

(116) Sell, C. S. Personal communication, Quest International, Ashford, Kent, UK; 1995.

(117) Amoore, J. E. In *Molecular Basis of Odor*; Kugelmass, I. N., Ed.; Charles C Thomas: Illinois, 1970.

(118) Beets, M. G. M. In *Structure-Activity Relationships in Human Chemoreception*; Applied Science Publishers Ltd: London, 1978; pp 154−155 and 246−247.

(119) Chastrette, M. *Chem. Senses* **1981**, *6*, 157.

(120) Chastrette, M.; Eminet, B. P. *Chem. Senses* **1983**, *7*, 293.

(121) Chastrette, M.; Cretin, D.; El Aïdi, C. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 108.

(122) Livingstone, D. In *Data Analysis of Chemical Data*; Oxford University Press: Oxford, UK, 1995; pp 205−217.
(123) Buchbauer, G.; Holbik, H.; Spreitzer, H.; Zechmeister-Machhart, F. In *Flavors and Fragrances: A World Perspective*; Proceedings of the 10th International Congress of Essential Oils, Fragrances and Flavors; Lawrence, B. M., Mookherjee, B. D., Willis, B. J., Eds.; Elsevier Science Publishers B. V.: Amsterdam, 1988; pp 833−840.
(124) Boelens, H.; Haring H. G. Personal communication, Naarden Int., Netherlands, 1981.
(125) Werner, H. *Fette Seifen* **1938**, *45*, 623.
(126) Boelens, H.; Punter, P. In *Third ECRO Congress*; European Chemoreception Research Organization: Pavia, Italy, 1978; pp 1−9.
(127) Sell, C. S.; Dorman, L. A. *Perfum. Flavor.* **1983**, *8* (2), 68.
(128) Sell, C. S.; Cairns, P. *Perfum. Flavor.* **1983**, *7* (6), 14.
(129) Boelens, M.; Wobben, H. J.; Heydel, J. *Perfum. Flavor.* **1980**, *5* (6), 2.
(130) Boelens, H.; Heydel J. *Chem. Ztg.* **1973**, *97*, 8.
(131) Berends, W.; van der Linde, L. M. *Perfum. Essent. Oil Rec.* **1967**, 372.
(132) Dorsky, J.; Easter, W. M., Jr. US 2976321, 1961; *Chem. Abstr.* **1961**, *55*, 16485h.
(133) Pelzer, R.; Harder, U.; Krempel, A.; Sommer, H.; Surburg, H.; Hoever, P. In *Recent Developments of Flavor and Fragrance Chemistry*; Proceedings of the 3rd International Haarmann & Reimer Symposium; Hopp, R., Mori, K., Eds.; VCH Publishers: Weinheim, Germany, 1993; pp 29−67.
(134) Ohloff, G.; Giersch, W. *Helv. Chim. Acta* **1980**, *63*, 76.
(135) Anselmi, C.; Centini, M.; Mariani, M.; Sega, A.; Pelosi, P. *J. Agric. Food Chem.* **1992**, *40*, 853.
(136) Anselmi, C.; Centini, M.; Mariani, M.; Sega, A.; Pelosi, P. *J. Agric. Food Chem.* **1993**, *41*, 781.
(137) Napolitano, E.; Giovani, E.; Centini, M.; Anselmi, C.; Pelosi, P. *J. Agric. Food Chem.* **1994**, *42*, 1332.
(138) Anselmi, C.; Centini, M.; Napolitano, E.; Pelosi, P.; Scesa, C.; Sega, A. *Int. J. Cosmet. Sci.* **1996**, *18*, 67.
(139) Winter, M.; Skouroumounis, G. *Helv. Chim. Acta* **1996**, *79*, 1095.
(140) Wannagat, U.; Damrath, V.; Harder, U. *Monatsh. Chem.* **1994**, *125*, 1159.
(141) Wannagat, U. *Nachr. Chem. Tech. Lab.* **1984**, *32* (8), 717.
(142) Wannagat, U.; Muenstedt, R. *Liebigs Ann. Chem.* **1985**, *5*, 944.
(143) Wannagat, U.; Muenstedt, R.; Harder, U. *Liebigs Ann. Chem.* **1985**, *5*, 950.
(144) Wannagat, U.; Damrath, V.; Schliephake, A.; Harder, U. *Monatsch. Chem.* **1987**, *118* (6−7), 779.
(145) Wannagat, U.; Damrath, V.; Huch, V.; Veith, M.; Harder, U. *J. Organomet. Chem.* **1993**, *443* (2), 153.
(146) Tang, S.; Li, Y.; Cao, Y.; Wang, X. *Chin. J. Chem.* **1991**, *9* (1), 68.
(147) Tang, S.; Xue, J.; Duan, M.; Cao, Y.; Zhi, J.; Wang, W. *Chem. Res. Chin. Univ.* **1993**, 9 (2), 127.
(148) Tang, S.; Xue, J.; Wu, J.; Cao, Y.; Zhi, J. *Chem. Res. Chin. Univ.* **1993**, *9* (2), 121.
(149) Matsuda, H.; Yamamoto, T.; Kanisawa, T. In *Flavors, Fragrances and essential Oils*; Proceedings of the 13th International Congress of Flavors, Fragrances and Essential Oils; Başer, K. H. C, Eds.; AREP Pub.: Istanbul, Turkey, 1995; Vol. 3, pp 85−91.
(150) Yoshii, F.; Hirono, S.; Moriguchi, I. *Helv. Chim. Acta* **1993**, *76*, 2279.
(151) Ogura, S.; Matsuda, H.; Yamamoto, T. Japanese Patent 5112484, 1993; *Chem. Abstr.* **1993**, *119*, 226221.
(152) Arctander, S. In *Perfume and Flavor Chemicals*; published by the author: Montclair, NJ, 1969.
(153) McGugan,W. A. *Food Res. Rep.* **1980**, *4* (1), 13.
(154) Forster, M. O.; Cardwell, D. *J. Chem. Soc.* **1913**, *103*, 1342.
(155) Dupont, J.; Labaune, L. *Chem. Zentralbl.* **1910**, *II*, 734.
(156) Von Braun, J.; Kröper, H. *Chem. Ber.* **1929**, *62B*, 2880.
(157) Boelens, H.; Heide, R.; Rijkens, F. *Am. Perfum. Cosmet.* **1968**, *83*, 27.
(158) Sell, C. S. *Seifen, Öle, Fette, Wachse* **1986**, *112* (8), 267.
(159) Sell, C. S. In *Flavors and Fragrances: A World Perspective*; Proceedings of the 10th International Congress of Essential Oils, Fragrances and Flavors; Lawrence, B. M., Mookherjee, B. D., Willis, B. J., Eds.; Elsevier Science Publishers B. V.: Amsterdam, Netherlands, 1988; pp 777−795.
(160) Boelens, H.; van der Linde, L. M.; de Rijke, D.; de Valois, P. J.; van Dort, J. M.; Takken, H. J. *Chem. Soc. Rev.* **1978**, *7* (2), 167.
(161) Rossiter, K. J. *Perfum. Flavor.* **1996**, *21* (2), 33.
(162) Cramer, R. D., III; Patterson, D. E.; Bunce, J. D. *J. Am. Chem. Soc.* **1988**, *110*, 5959.
(163) Charton, M. *J. Am. Chem. Soc.* **1967**, *91*, 615.
(164) Charton, M. *J. Org. Chem.* **1979**, *44*, 2284.
(165) Cerveny, L.; Krivska, M.; Marhoul, A.; Pokorny, J.; Kalinova, J. *Perfum. Flavor.* **1993**, *18* (6), 41.
(166) Takeoka, G. R.; Buttery, R. G.; Turnbaugh, J. G.; Teranishi, R. *Lebensm.-Wiss. u. Technol.* **1991**, *24*, 569.
(167) Boelens, M. H.; van Gemert, L. J. *Perfum. Flavor.* **1993**, *18* (3), 29.
(168) Polak, E.; Fetison, G.; Fombon, A. M.; Skalli, A. *J. Agric. Food Chem.* **1988**, *36*, 355.
(169) van der Weerdt, A. J. A. In *Flavors and Fragrances: A World Perspective*; Proceedings of the 10th International Congress of Essential Oils, Fragrances and Flavors; Lawrence, B. M., Mookherjee, B. D., Willis, B. J., Eds.; Elsevier Science Publishers B. V.: Amsterdam, Netherlands, 1988; pp 405−414.
(170) Morris, A. F. *Perfum. Flavor.* **1981**, *6* (1), 1.
(171) Clark, G. S. *Perfum. Flavor.* **1990**, *15* (4), 47.
(172) Bedoukian, P. Z. *Am. Perfum. Cosmet.* **1963**, *87* (12), 31.
(173) Hatanaka, A.; Kajiwara, T.; Matsui, K. *Z. Naturforsch.* **1995**, *50* (7/8), 467.
(174) Panten, J. *SOFW J.* **1995**, *121* (9), 641−646; 648−649.
(175) Woerner, P. *SOFW J.* **1995**, *121* (9), 652−4; 657.
(176) Bedoukian, P. Z. *J. Agric. Food. Chem.* **1971**, *19*, 1111.
(177) Hatanaka, A.; Kajiwara, T.; Horino, H.; Inokuchi, K. *Z. Naturforsch.* **1992**, *47* (3−4), 183.
(178) Vasil'ev, A. A.; Cherkaev, G. V; Nikitina, M. A. *Mendeleev Commun.* **1995**, 115.
(179) Carpenter, M. S. *Proc. Sci. Sect. Toilet Goods Assoc.* **1955**, *23*, 1.
(180) Ledener, E. *Fortschr. Chem. Org. Naturst.* **1950**, *6*, 87.
(181) Mookherjee, B. D.; Wilson, R. A. In *Fragrance Chemistry - The Science of the Sense of Smell*; Theimer, E. T., Ed.; Academic Press: New York, 1982; pp 434−494.
(182) Wood, T. F. In *Fragrance Chemistry - The Science of the Sense of Smell*; Theimer, E. T., Ed.; Academic Press: New York, 1982; pp 495−507.
(183) Bauer, A. *Chem. Ber.* **1891**, *24*, 2836; German Patents 47599, 1888; 62362, 1891; *Beilstein Handbook Organic Chemistry Hauptwerk*, Vol. 5, p 436.
(184) Carpenter, M. S.; Easter, W. M., Jr. *J. Org. Chem.* **1951**, *16*, 586; US Patent 2450878, 1948; *Chem. Abstr.* **1949**, *43*, 1063g.
(185) Dyson G. M. *Perfum. Essent. Oil Res.* **1927**, 75.
(186) Beets, M. G. J. In *Structure-Activity Relationships in Human Chemoreception*; Applied Science Publishers Ltd: London, 1978; pp 207−245.
(187) Hill, J. W.; Carothers, W. H. *J. Am. Chem. Soc.* **1933**, *55*, 5039.
(188) Spanagel, E. W.; Carothers, W. H. *J. Am. Chem. Soc.* **1935**, *57*, 929.
(189) Ruzicka, L.; Stoll, M. *Helv. Chim. Acta* **1934**, *17*, 1308.
(190) Stoll, M. *Drug Cosmet. Ind.* **1936**, *38*, 334.
(191) Ohloff, G.; Becker, J.; Schulte-Elte, H. K. *Helv. Chim. Acta* **1967**, *50*, 705.
(192) Davies, J. T.; Theimer, E. T. *J. Agric. Food Chem.* **1967**, *15*, 6.
(193) Klouwen, M. H.; Kok, J. G. J.; Ruys, A. H. *J. Soc. Cosmet. Chem.* **1963**, *14*, 19.
(194) Bauer, K. A., Korber, A. K. In *Proceedings of the 2nd International Haarman & Reimer Symposium on Flavor and Fragrance substances*; D & PS Verlag: Pattensen, Fed. Rep. Ger., 1980; pp 129−35
(195) Prelog, V.; Ruzicka, L. *Helv. Chim. Acta* **1944**, *27*, 61.
(196) McAndrew, B. A.; Russell, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1172.
(197) Bersuker, I. B.; Dimoglo, A. S.; Gorbachov, M. Yu.; Vlad, P. F. *New J. Chem.* **1991**, *15*, 307.
(198) Prelog, V. *J. Chem. Soc.* **1950**, 420.
(199) Bernardinelli, G.; Gerdil, R. *Helv. Chim. Acta* **1982**, *65*, 558.
(200) Bernardinelli, G.; Gerdil, R. *Helv. Chim. Acta* **1982**, *65*, 730.
(201) Bernardinelli, G.; Gerdil, R. *Helv. Chim. Acta* **1982**, *65*, 1310.
(202) Beets, M. B. J. *Am. Perfum.* **1961**, 54.
(203) De Ridder, D. J. A.; Schenk, H. In *QSAR: Rational Approaches to the Design of Bioactive Compounds*; Elsevier Science Publishers B. V.: Amsterdam, 1991; pp 301−304.
(204) Ham, C. L.; Jurs P. C. *Chem. Senses* **1985**, *10*, 491.
(205) Chastrette, M.; Zakarya, D.; Elmovaffek, A. *Eur. J. Med. Chem.* **1986**, *21* (6), 505.
(206) Chastrette, M.; De Saint Laumer, J. Y.; Peyraud, J. F. *SAR QSAR Environ. Res.* **1993**, *1* (2−3), 221.
(207) Chastrette, M.; Zakarya, D.; Peyraud, J. F. *Eur. J. Med. Chem.* **1994**, *29*, 343.
(208) Boelens, H.; Traas, P. C.; Takken, H. J. *Perfum. Flavor.* **1980**, *5* (1), 39.
(209) Schlosser, M.; Shi, G; Cottens, S.; Shiba, S. A. *Tetrahedron* **1992**, *48*, 10569.
(210) Fráter, G.; Müller, U.; Bajgrowicz, J. A.; Petrzilka, M. In *Flavors, Fragrances and Essential Oils*; Proceedings of the 13th International Congress of Flavors, Fragrances and Essential Oils; Başer, K. H. C, Ed.; AREP Publ.: Istanbul, Turkey, 1995; Vol. 3, pp 151−159.
(211) Fehr, C.; Galindo, J.; Haubrichs, R.; Pernet, R. *Helv. Chim. Acta* **1989**, *72*, 1537.
(212) De Ridder, D. J. A.; Ćapková, P.; Hatjisymeon, K.; Fraanje, J.; Schenk, H. *Acta Crystallogr.* **1994**, *B50*, 607.
(213) Chastrette, M.; Zakarya, D. *C. R. Acad. Sci. Paris, Série II* **1988**, *307*, 1185.
(214) Narvaez, J. N.; Lavine, B. K.; Jurs, P. C. *Chem. Senses* **1985**, *10*, 145.
(215) Klopman, G.; Ptchelintsev, D. *J. Agric. Food Chem.* **1992**, *40*, 2244.

(216) Yoshii, F.; Liu, Q.; Hirono, S.; Moriguchi, I. *Chem. Senses* **1991**, *14*, 319.
(217) Jain, A. N.; Dietterich, T. G.; Lathrop, R. H.; Chapman, D.; Critchlow Jr. R. E.; Bauer, B. E.; Webster, T. A.; Lozano-Perez, T. *J. Comput. Aided Des.* **1994**, *8*, 635.
(218) Beets, M. G. J. In *Molecular Structure and Organoleptic quality*; Society of Chemical Industry: London, 1957; p 54.
(219) Jurs, P. C.; Ham, C. L. *J. Agric. Food Chem.* **1977**, *25*, 1158.
(220) Brunke, E. J. *Dragoco Rep.* **1983**, 139.
(221) Marmor, R. S. *Perfum. Flavor.* **1983**, *8* (4), 37.
(222) Weyerstahl, P; Brende, J.; Glasow, L. *Flavour Fragance J.* **1992**, *7*, 1.
(223) Weyerstahl, P.; Schneider, K. *Liebig Ann. Chem.* **1992**, 1049.
(224) Teisseire, P.; Maupetit, P.; Corbier, B.; Rouillier, P. *Recherches* **1974**, *19*, 36.
(225) Näf, F.; Decorzant, R.; Giersch, W.; Ohloff, G. *Helv. Chim. Acta* **1981**, *64*, 1387.
(226) Spreitzer, H. *Helv. Chim. Acta* **1990**, *73*, 1730.
(227) Mookherjee, B. D.; Light, K. K.; Hill, I. D. In *Essential Oils*; Mookherjee, B. D., Mussinan, C. J., Eds.; Allured Publishing Corp.: Wheaton, IL, 1981; pp 247−272.
(228) Weyerstahl, P.; Splittgerber, H. D.; Walteich, J.; Wollny, T. *J. Essent. Oil Res.* **1989**, *1*, 1.
(229) Spreitzer, H. *Monatsh. Chem.* **1992**, *123*, 587.
(230) Weyerstahl, P.; Gansau, C.; Claussen, T. *Flavour Fragance J.* **1991**, *6*, 1.
(231) Weyerstahl, P.; Gansau, C.; Marschall, H. *Flavour Fragance J.* **1993**, *8*, 297.
(232) Finato, B.; Lorenzi, R.; Pelosi, P. *J. Agric. Food Chem.* **1992**, *40*, 857.
(233) Brunke, E. J. *Dragoco Rep.* **1981**, 251.
(234) Brunke, E. J.; Klein, E. In *Fragrance Chemistry - The Science of the Sense of Smell*; Theimer, E. T., Ed.; Academic Press: New York, 1982; pp 397−431.
(235) Erman, W. F. *J. Am. Chem. Soc.* **1964**, *86*, 2887.
(236) Demole, E. *Helv. Chim. Acta* **1964**, *47*, 319.
(237) Demole, E. *Helv. Chim. Acta* **1964**, *44*, 1766.
(238) Demole, E. *Helv. Chim. Acta* **1969**, *52*, 2065.
(239) Ansari, H. R.; Jaggers, B. G.; Jones, B. N.; Janes, J. F. Dt. Offenleg. 2,255,199, 1973; U.S. Patent, US 3,963,648 (15-6-76); equivalent to U.S. Patent, US 3,963,648 (12-11-71); *Chem. Abstr.* **1973**, *79*, 41918e.
(240) Ansari, H. R.; Curtis, A. J. *J. Soc. Cosmet. Chem.* **1974**, *25*, 203.
(241) Naipawer, R. E.; Purzycki, K. L.; Shaffer, G. W.; Erickson, R. E. In *Essential Oils*; Mookerjee, B. D, Mussinan, C. J., Eds.; Allured Publishing Corp.: Wheaton, IL, 1981; pp 105−133.
(242) Sukh Dev. *Proceedings of the 11th Int. Congr. Essent. Oils, Fragrances & Flavors*; Bhattacharyya, S. C., Sen, N., Sethi, K. I., Eds.; Oxford & IBH Publishing Co. Pvt. Ltd.: New Delhi, India, 1989; Vol. 2, pp 1−12; *Chem. Abstr.* **1992**, *117*, 178071/18.
(243) Gora, J.; Gibka, J. *Perfum. Flavor.* **1995**, *20* (6), 19.
(244) Witteveen, J. G.; van der Weerdt, A. J. A. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 29.
(245) Becker, A.; Beyer, A.; Buchbauer, G.; Pranka, E.; Wolschann, P. *Monatsh. Chem.* **1988**, *119*, 711.
(246) Buchbauer, G.; Becker, A.; Winiwarter, S.; Beyer, A.; Wolschann, P. In *Proceedings of the 11th Int. Congr. Essent. Oils, Fragrances & Flavors*; Bhattacharyya, S. C., Sen, N., Sethi, K. I., Eds.; Oxford & IBH Publishing Co. Pvt. Ltd.: New Delhi, India, 1989; Vol. 5, pp 1−10; *Chem. Abstr.* **1992**, *117*, 128801/13.
(247) Becker, A.; Beyer, A.; Buchbauer, G.; Winiwarter, S.; Wolschann, P. *Flavour Fragance J.* **1988**, *3*, 173.
(248) Buchbauer, G.; Becker, A.; Winiwarter, S. *J. Essent. Oil Res.* **1990**, *2*, 221.
(249) Becker, A.; Buchbauer, G.; Winiwarter, S.; Wolschann, P. *Monatsh. Chem.* **1992**, *123*, 405.
(250) Buchbauer, G.; Winiwarter, S.; Wolschann, P. *J. Comput.-Aided Mol. Des.* **1992**, *6*, 583.
(251) Buchbauer, G.; Leonhardsberger, K.; Winiwarter, A.; Wolschann, P. *Helv. Chim. Acta* **1992**, *75*, 174.
(252) Buchbauer, G.; Stock, A.; Weiss, P.; Winiwarter, S.; Wolschann, P. *Z. Naturforsch.* **1992**, *47b*, 1759.
(253) Buchbauer, G.; Neumann, A.; Siebenheitl, U.; Weiss, P.; Wolschann, P. *Monatsh. Chem.* **1994**, *125*, 747.
(254) Buchbauer, G.; Hillisch, A.; Mraz, K.; Wolschann, P. *Helv. Chim. Acta* **1994**, *77*, 2286.
(255) Neumann, A.; Wei, P.; Wolschann, P. *J. Mol. Struct.* **1993**, *296*, 145.
(256) Krotz, A.; Helmchen, G. *Tetrahedron. Asymmetry*, **1990**, *1*, 537.
(257) Buchbauer, G.; Spreitzer, H.; Swatonek, H.; Wolschann, P. *Tetrahedron: Asymmetry* **1992**, *3*, 197.
(258) Chastrette, M.; Zakarya, D.; Pierre, C. *Eur. J. Med. Chem.* **1990**, *25*, 433.
(259) Aulchenko, I. S.; Beda, A. A.; Dimoglo, A. S.; Gorbachov, M. Yu.; Kheifits, L. A.; Shvets, N. M. *New J. Chem.* **1995**, *19*, 149.
(260) Aulchenko, I.; Dimoglo, A.; Güzel, Y.; Kheifits, L.; Saripinar, E.; Shvets, N.; Yildirim, I. *Flavors, Fragrances and Essential Oils*; Proceedings of the 13th International Congress of Flavors, Fragrances and Essential oils; Başer, K. H. C., Ed., AREP Publ.: Istanbul, Turkey, 1995; Vol. 3, pp 29−38.
(261) Buchbauer, G.; Spreitzer, H.; Oeckher, B.; Pretterklieber, C.; Piringer, I.; Wolschann, P. *Monatsch. Chem.* **1995**, *126*, 467.
(262) Buchbauer, G.; Lebada, P.; Spreitzer, H.; Wolschann, P. *Liebigs Ann.* **1995**, *9*, 1693.

CR950068A