The Relation of Structure and Odor in Substituted Cyclohexanols

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The correlation of chemical structure and odor has been a puzzling problem for chemists as well as perfumers since the emergence of synthetic aromatic chemicals for over 100 years. Several theories have been proposed to model the interaction between an odorous chemical substance and a receptor expected to be directly at the nerve ends in the regio olfactoria.

One generally accepted explanation[1] assumes a correlation between a basic shape of the molecule and its prevalent odor character in analogy to the classical key-lock interaction between an active agent and its receptor site. This does not interfere with theories which assume that the same molecule may bind to several receptor sites, thereby generating a varied i.e. "mixed" response to explain the seemingly endless multitude of olfactorial perceptions.

All of the current theories lack a biochemical foundation and knowledge of the true geometry of the receptor site in the olfactory bulbus. This and a still unexplained fact that not only diverse chemical structures but also analogues of a similar basic structure sometimes smell quite differently is one of the reasons we still need more information about the correlations between different chemical structures and their odor perceptions.

In this context one must never forget that the perception of odor—as all of us know—is fairly subjective. This had led some researchers to an approach of using odor difference recognition[2] as the tool rather than the classical odor description with interesting results. However, again it falls short of being generally applicable.

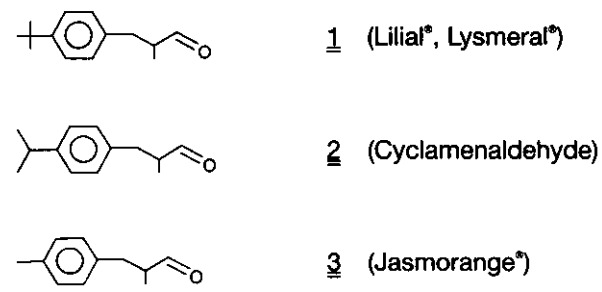

Figure 1. Examples of close structural similarities of odors.

A few examples of close structural similarity are given in Figure 1. The only variation is in the p-alkyl substituent. Superficially these odors might be described as floral; all are somewhat related to a lilly of the valley odor. However, such crude classification is neglecting the necessary refinement required for perfumery. Therefore the real odor descriptions are quite diverse and the products established aroma chemicals in very different fields of perfumery.

Another basic structure which yields diverse odor perceptions is cyclohexanol. Cyclohexanol itself is of little importance in perfumery. It has a camphoraceous, chemical odor and is used only occasionally as a masking component in technical perfumery. Through esterification the odor is changed, resulting in a pleasant fruitiness. Despite their chemical simplicity they have never become important for the perfumer.

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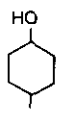
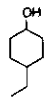
4 camphoraceous, slightly minty

5 camphoraceous, slightly minty

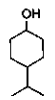


6 camphoraceous

Figure 2. Methyl cyclohexanols

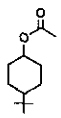


7 chemical, pungent, gassy



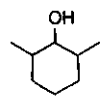
8 camphoraceous, geranium-like

9 camphoraceous, woody, patchouli-like

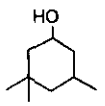


10 woody

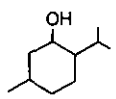
Figure 3. Monoalkyl cyclohexanols



11 camphoraceous, minty, herbal

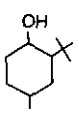


12 camphoraceous, minty



13 minty

Figure 4.Dialkyl cyclohexanols



14

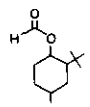
Figure 5. 2-t-Butyl-4-methyl-cyclohexanol (Rootanol)

14a camphoraceous, sweet, minty

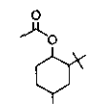
14b camphoraceous, root-like

14c minty, camphoraceous

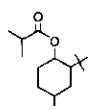
Figure 8. Rootanol Isomers



15 woody



16 woody, tobacco, fruity, musky



17 woody, balsamic, fruity

Figure 6. Ester derivatives

The structure-odor correlation of substituted cyclohexanols became recently of interest to us and led us to explore their chemistry and olfactorial properties.

Substitution Variations

Figure 2 lists methyl-substituted cyclohexanols and their odor profiles. Methylcyclohexanols exhibit basically a camphoraceous odor but have a less chemical, fresher character than the unsubstituted cyclohexanol itself. The substitution position has only a minor influence on the odor.

Variation of the alkyl group changes the basic camphor theme in parallel with increasing complexity of the substitutent (Figure 3). The p-ethyl derivative [7] has a very chemical pungent, but still camphoraceous odor. It is not used in perfumery.

p-Isopropyl-cyclohexanol [8] modifies the camphoraceous odor with floral, geranium-like side notes. The p-tert-butyl-cyclohexanol [9] is differentiated by woody, patchouli-like notes over the basic camphor type. An increasing complexity of the substituent corresponds nicely to a greater odor differentiation versus the base molecule cyclohexanol.

Interestingly the camphoraceous character disappears completely by esterification of the last product [9]. p-tert-Butycyclohexyl acetate [10] together with the corresponding ortho-isomer are well established products in perfumery and preferred for their woody and fruity character.

With the introduction of a second alkyl group to the cyclohexanol ring the odor becomes more complex and starts to exhibit minty notes (Figure 4). 2,5-Dimethylcyclohexanol [11] demonstrates a combination of the camphoraceous and minty character with a herbal note. The trisubstituted 3,3,5-trimethylcyclohexanol [12] is already quite reminiscent of the volume-wise most important substituted cyclohexanol, i.e. menthol [13] despite its structural difference.

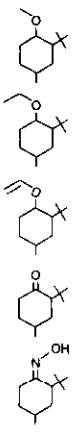
The menthol stereoisomers are a good but still unexplained example of the correlation between molecular geometry and odor. All 8 possible isomers exhibit different odor profiles. Some like the 1-menthol have a pure minty odor whereas others lean more to the camphoraceous side.

We have recently synthesized a variety of structures with a similar substitution pattern as menthol. The basic molecule is 2-butyl-4-methyl-cyclohexanol [14] (Figure 5). A basic fresh, camphoraceous-minty character is modified by earthy notes. Because these earthy undertones remind of vetiver or ginseng roots the molecule was named Rootanol. This product is synthesized through hydrogenation of its aromatic precursor resulting in a mixture of isomers. Expectedly these isomers differ in their odor. Some correlations between the molecular geometry and the respective odor types could be obtained.

The isomeric mixture consists mainly of 2 out of the 4 possible isomers (Figure 8). While [14a] has a camphoraceous-minty character with a slight sweetness in the tail, the other main isomer [14b] is responsible for the root-like character. The odor of the minor isomer [14c] is again minty camphoraceous. The theoretically possible forth isomer is energetically unfavoured and therefore present only in trace; apparently it does not contribute to the odor profile.

As in the case of many cyclohexanols the molecule is very stable and can be used even under adverse conditions as high alkalinity or acidity.

In contrast to simple cyclohexanol esters ester derivatives of Rootanol do not have so much a fruity character but rather a woody one. Figure 6 depicts a



18 floral, fruity, earthy

19 floral, fruity, earthy

20 woody, earthy, minty

21 camphoraceous, terpene-like, fruity

22 woody, minty

Figure 7. Ether derivatives

few esters. The formate [15] has a warm, woody odor and is reminiscent of decalinyl formate.

Changing the ester from the formate to the acetate [16] seems to have little bearing on the basic woody character at first. However a more detailed odor evaluation reveals that the woody note tends now toward a musky, damascone-like odor; to this character are added tobacco and fig-notes. Altogether the complex character renders such a simple derivative quite useful for oriental and floral perfumes as well as chypre variations and thereby has a profound effect on the usefulness in perfumery.

With increasing length of the acid moiety the woody character remains basically unchanged. In the propionate [17] one can recognize a shift to a more balsamic note, with a secondary fruity note. Esters of higher acids become more and more balsamic, while the fruity note remains, concurrent with a weakening of odor strength, as expected for a higher molecular weight.

Other variations of the base molecule are ethers (Figure 7). The methyl and ethyl ether of Rootanol [18 and 19] are very much alike, quite corresponding to their close structural similarity. They show a floral, fruity odor with still an earthy note. The vinyl ether [20] is woody, earthy with a minty undertone. The oxidation to the ketone [21] yields an odor again in the camphoraceous field with terpene-like undertones. The introduction of more heteroatoms—without changing the bulkiness of the group—i.e. the oxime [22]—varies again the basic character. The odor of the oxime reminds strongly of Rootanol, but has a more profound woodiness.

Applications

It can be concluded, that ether derivatives do not change the odor characteristics of Rootanol dramatically, but rather add more variations to the basic theme. However in the search for new aroma chemicals, odor differences considered small from the perspective of a synthetic chemist may turn out decisive for the nose of the discriminating perfumer.

Alpha amyl cinnamic aldehyde	30
Cinnamic alcohol	20
Heliotropine	20
Geraniol	130
Benzyl acetate	110
Terpineol	100
Phenylethyl alcohol	40
Linalool	60
Aldehyde C_{14}	3
Isoeugenol	3
Galaxolide® 50	24
Jasmine	20
Lysmeral	50
Methyl ionone	60
Balinol®	10
Lavandin oil grosso	80
Citronellyl nitrile	10
p-t Butyl-cyclohexyl acetate	80
ROOTANOL® 50	40
Diethyl phthalate	110
	1000

Application: soap, detergent etc.

Figure 9. Floral accord

To examine this aspect closely, a brief consideration of the impact of Rootanol on a perfume compound is required. The earthy, root-like character is coming out clearly in a compound such as Figure 9. In this compound the root-like character is better detectable than in the pure Rootanol. The basic floral, spicy character of the compound gains noticeably in freshness by the addition of 4% Rootanol in the form of a 50% solution in DEP. The woody note is strengthened and lends more complexity to the formula. Such formula may be used in a soap or detergent.

The example in Figure 10 is an application test of a pine compound as one may use in a shampoo. Here not so much a direct contribution of the root-character of the aroma chemical is observed, but rather an important change of the pine note: it is enhanced. In pine notes a much higher level of Rootanol can be used.

In both examples the addition of Rootanol makes the compound far more radiant and increases the value of the perfume accordingly. This may seem surprising, as at a first glance one does not readily expect a "bass note" i.e. the root-like character to strengthen the "soprano" voices in a "pine concert".

Isobornyl acetate	160
Terpentine oil	180
Pine needle oil Siberian	140
Aldehyde C_{12} MNA	10
Terpinyl acetate	150
Borneol crist.	20
Dipentene	100
Galaxolide® 50	20
Cedarwood oil Florida	30
Coumarin	15
Olibanum resin	15
Linalool	15
Aldehyde C_{12} Lauric (10% in DPG)	20
Styrolyl acetate	5
Terpineol	40
ROOTANOL 50	80
	1000

Application: shampoo, shower gel. etc.

Figure 10. Pine accord

Dipentene	400
Ethyl acetoacetate	120
Decyl acetate	50
Citronellyl nitrile	60
Styrolyl acetate	15
Aldehyde C_{14} 10% in DPG	20
Diphenyl oxide	20
Hexyl benzoate	50
Benzyl acetate	25
Dimethyl heptanol	40
Jasmorange®	40
Aldehyde C_{12} MNA 10% in DPG	50
ROOTANOL® 50	40
Dipropylene glycol	70
	1000

Application: chlorine bleach etc.

Figure 11. Lemon accord

The versatility is proved by another example (Figure 11) in which the addition of a small amount of Rootanol increases the radiance and freshness of this simple lemon accord. Because of the excellent stability the usage in aggressive media poses no problem; thereby such compound may be used in bleaches or other harsh cleansing products.

The stability of Rootanol has been tested in several common consumer products (Figure 12). The chemical nature renders the molecule stable in almost all media. Although stability is demanded today of many formulations, still the availability of truly stable economical aroma chemicals represents a problem to the perfumer. Rootanol may help to alleviate this problem.

pH 1–12
Detergent (perborate)
Detergent (TAED)
Chlorine bleach
Antiperspirants
Cold wave
Soap
Shampoo

– stable in all media above

Figure 12. Stability data Rootanol

Conclusions

The relation of the chemical structure of a number of derivatives of 2-t-butyl-4-methyl-cyclohexanol (Rootanol) to their odor characteristics has been elucidated. Products with a free alcohol group exhibit primarily a minty or camphoraceous odor. However the side notes of these derivatives reveal quite interesting novel odor patterns. The root-like odor of Rootanol is an odor facet which can yield quite remarkable results when incorporated into perfume compounds.

Ester derivatives of Rootanol show woody notes as observed for some other cyclohexanol esters, however the woodiness is more profound and less accompanied by chemical side notes rendering these derivatives more interesting to perfumers than previously known cyclohexanol esters.

A detailed evaluation of the odor value of several cyclohexanol derivatives reveals that a structure-odor approach is of limited value for odor prognosis yet, as minor subtleties in the odor profile influence the usefulness of an aroma chemical to the perfumer greatly.

The observation of woody and root-like notes in this chemical family will spurn not only further synthetic work but may also serve ultimately to enlarge the compendium of available tools for the creative work of the perfumer.

References

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1. J E Amoore, *Molecular Basis of Odor*, C Thomas Publ., Springfield (1970)
2. E Polak, *Chem and Ind* **3**, 30 (1983)