Some Aspects of Qualitative Structure-Odor Relationships

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Qualitative odor-structure relationships have been applied for more than a century. The results of these studies are mostly the consequence (outcome) of the application of common sense gathered by experience. Two main features characterize the molecular structures of odorant molecules: "electronicity" (electronic charge distribution over a molecule) and "stereocity" (volume, shape and profile of a molecule). We will show herein that odorant molecules with similar structures possess similar odor qualities. Sometimes chemical functional groups (aldehyde-nitrile-nitro, acetyl-acetate) with similar electronicity can replace each other in odorants without disturbing the odor quality to a great extent. The same holds true for the substitution of sterical parts of the odoriferous molecules (phenyl-isobutenyl, cyclohexyl-isoamyl, sulfur-ethenyl, chloro-methyl), which determine stereocity.

History

For more than a century, attempts have been made to correlate the structures of odorant molecules with their olfactory responses. It seems worthwhile to review some important statements, concepts and theories that have been published over the last century.

In 1918, the Nobel Prize winner, Ruzicka, was already stating: molecular shape determines the character of an odoriferous substance, while the osmophoric (functional) group only causes variations in its character.[1]

Dyson was the first to mention that odoriferous properties of molecules were based on infrared vibrations.[2] Amoore introduced, in 1952, an odor theory based on the molecular size and shape of the odorants.[3a] He proposed that the odor of compounds can be classified on the basis of molecular shape and size, the shape and size factor being described in terms of matching into a shaped site. Later on, this theory was modified to the molecular parameters of a limited number of primary odorants.[3b,c] Davies and Taylor developed what is called the penetrating and puncturing theory of odor.[4] This theory assumes that, first, molecules have to go from the air into the lipid/water inter-phase on the mucus. For this penetration, the desorption/adsorption energy from air into a lipid/water layer is important. Second, the adsorbed molecules must be effective for stimulation of the olfactory nerve membrane via puncturing. Thus, for puncturing, the cross sectional area of the molecule is a dominating factor.

Starting in 1953, Wright studied the relationships between frequencies in far infrared adsorption spectra —"osmic active frequencies"— and the odor of the compounds.[5] In 1957, Beets introduced his profile-functional group concept for odorants.[6a] In this concept, he stated that the following were crucial for odor type: the overall molecular profile; the nature and accessibility of the main functional group; and the influence of the location of a second equivalent functional group.

Many organic chemists that study structure-odor relationships often maintain two guiding thoughts. The first is that of Beets, who said that the structure of an organic compound fully defines its chemical, physical and physiological properties, including the odor.[6b] The second, of Stoll, mentions that one should treat the relationship between structure and odor of only a few well-specified substances.[7]

Dravieks proposed an electron donor/acceptor type of interaction during human olfaction.[8] Shah et al. stated the necessity of the presence of delocalized π-electrons for odoriferous compounds.[9]

Voitkevich mentioned chemosorption of odorants with pigment molecules.[10] Smalley published work regarding energy transfer by nozzle excitation during odor perception.[11] Laffort et al. investigated olfactory coding on the basis of physicochemical properties.[12] This olfactory coding explains that the affinity of the

> The complete shape . . . of stereochemical configuration, and electronic charge-distribution over a whole molecule . . . can describe the structure of a chemical compound.

stimulus for the receptor depends on four molecular properties. These may be derived from retention indices in gas chromatography using four suitably selected stationary phases. The first is proportional to the volume of the molecule; the second, to the proton affinity; the third, to a local polarizibility; and the fourth to the proton donor ability. Ohloff developed the triaxial rule of odor sensation.[13] He stated that the specific site of the human olfactory receptor system is involved in a three-dimensional interaction with the stimulating substance. From observation of the molecular features of ambergris-type odorants, it could be recognized that they combine to give a specific odor impression. Conformational analysis has been applied to over 200 diastereoismeric compounds, helping to extend the basis of the triaxial rule of odor sensation. Chemists working in vitro tend to publish extreme examples of odorants and non-odorants (enantiomers, epimers), when in fact sensory properties are not so pronounced. These chemists, in our opinion, prefer to afford primary mechanisms of olfaction, which suits their findings, without being experts in this field. Most of the resultant theories or concepts are short-lived.[2-13] Moreover, these theories underestimate the importance of the behavioral effects.

In 1994, Mori and Shepherd published an odortype theory of odor perception in which different receptors bind to structural motifs of the odorant, and in which the pattern of receptor activation is interpreted by the brain to identify, in an unique way, the whole odorant molecule.[14] The main evidence for this theory is that identified receptor subtypes respond not to one, but to many odorants.

What is the situation of the art of structure-odor relationships today? Rossiter wrote in 1996: "It is noticeable that whatever odour 'rules' are deduced, there are always exceptions. The non-odoriferous exceptions are probably explained by steric hindrance to a receptor fit or lack of volatility, but compounds which have anomalous odour characteristics or intensities are not as easy to explain."[15a] In 1998, Frater et al. concluded that shape-based structure-odor relations still were in a "sorry" state.[16] In 2001, Sell mentioned, "There are many examples of cases where two very similar molecules elicit very different odour, yet a third molecule which apparently bears little structural resemblance to either of the first two, elicits an odour very similar to one of them."[17b] (See F-1.) Turin predicted the similarities in the odor character of different structural classes with his method for spectrum calculation (inelastic electron tunneling spectrscopy).[18a,b] Turin and Yoshii stated, "Neither theory, when faced with a novel molecule, is yet able to predict reliably what its odour character will be," and, "The fact that after several decades of experimental investigations the basic mechanism by which odours are detected remains open to question, shows that there is much work to be done."[18a] Our own studies about structure-odor relationships can be found in a number of publications.[19] Excellent books and other publications about molecular structures of odorants have appeared, mainly with respect to modern fragrance chemistry.[20-25]

The complete shape (form, volume, profile) of stereochemical configuration, and electronic charge-distribution over a whole molecule (including, for example, dielectrical constant and dipole moment) can describe the structure of a chemical compound. The complete stereochemical configuration of a molecule can be called its "stereocity," and the complete electronic charge-distribution its "electronicity." In future studies we will demonstrate that isosteric (resembling stereocity) and iso-electronic (resembling electronicity) molecules can reveal a certain resemblance in odor character. Some examples of isosteric compounds are isobutenyl- and phenyl groups, and isoamyl and cyclohexyl derivatives; examples of iso-electronic compounds are aldehyde and nitrile groups, and methyl esters and methyl ketones. Several examples of isosteric and iso-electronic aroma chemicals are commercial commercially available today.

> . . . [I]so-electronicity of different odorant molecules . . . may lead to similar odor qualities, and isostereocity of different odorant molecules . . . also afford reminiscent odor qualities.

In this study, we will demonstrate that: iso-electronicity of different odorant molecules — molecules with more or less the same electron donor/

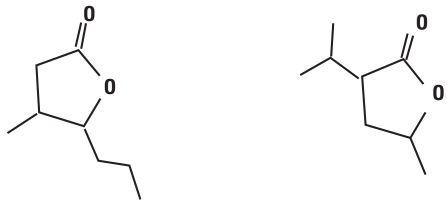
acceptor interaction and polarizability (as can be measured by dielectrical constants in dipole moments) — may lead to similar odor qualities, and that isostereocity of different odorant molecules — molecules with more or less the same volume, shape and profile — also afford similar odor qualities (F-2).

Although various groups of odorants possessing different molecular structures, yet with a certain iso-electronicity and isostereocity, may have similar odor qualitities and other psychophysical properties, such as tenacity; however, fiber-, hair- and skin-substantivity can be quite different, due to the variations in volatility (boiling point) and the presence of more π-electrons (e.g. phenyl versus isobutenyl).

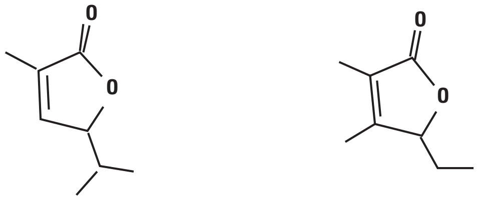
This study was initiated by the fact that more and more isosterical and iso-electronical aroma chemicals are commercialized today.

Similar molecular structures with differing olfactive qualities

F-1



lactonic (coconut-like) minty (menthone-like)



herbaceous (carvone-like) aromatic-spicy (celery-like)

powerful aromatic (maggi-like) mild lactonic

strongly fruity (stawberry-like) weakly acidic (virtually odorless)

Discussion

One might question whether investments in structure-activity investigations are worth the cost. Or more precisely, one might ask, “Do industrial research, in general, and studies on structure-activity relationships, in particular, afford an economic return on investment?” Recent studies by the American Council for Chemical Research revealed that during the period of 1975-1998, every US dollar invested by 83 chemical industries gave a brute profit (pay-out or return-on-investment) of $2.60. In conclusion: research in the chemical industry does pay off. To develop a new drug, dye, herbicide, lubricant or aroma chemical, investigation of structure-activity-relationships can be useful/helpful.

We argue that, indeed, it is necessary.

The reasons for studying odor-structure relationships can be, for instance, to produce an aroma chemical (flavor or fragrance material) with: modified, new or unknown sensory properties (e.g. concerning odor quality and appreciation); more odor value for the money (e.g. longlastingness, tenacity, persistence); improved physiological properties (e.g. better biodegradability, less toxicity); better application properties (e.g. fiber, hair and skin substantivity); and improved physicochemical properties (e.g. chemical stability, desired volatility and solubility).

Substitution of Isobutenyl by Phenyl in Monoterpenoids

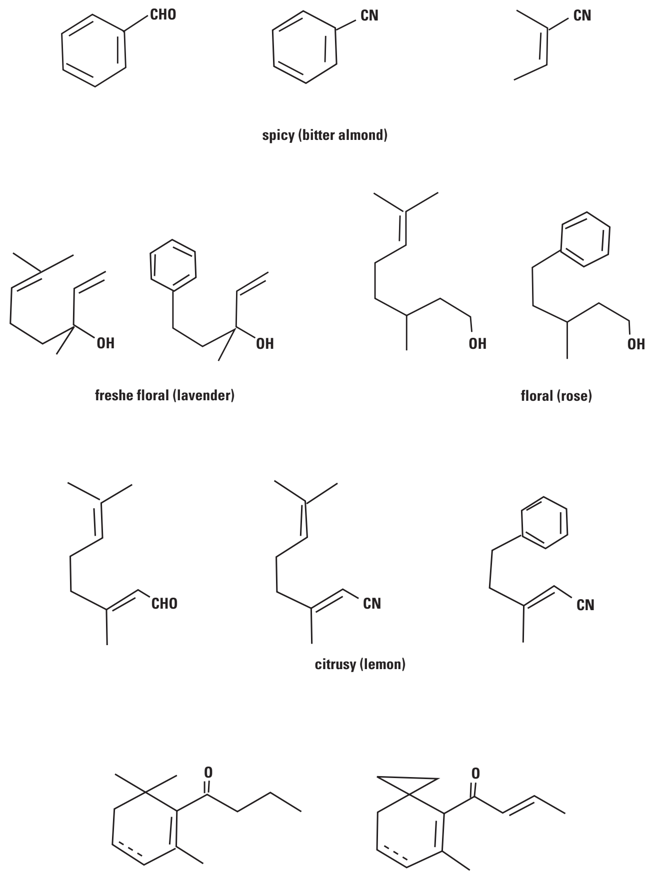
Various examples of the replacement of an isobutenyl group with a phenyl group are given in the literature.

Substitution of the butenyl group by a phenyl group has little effect on the odor character of linalool, rose oxide and geranonitrile. Turin predicted this with his method for spectrum calculation (inelastic electron tunneling spectroscopy) of the similarities in odor character of different structural classes. The isobutenyl part in the original molecules is more vulnerable to oxidation than the phenyl part in substituted molecules. Whereas the odor qualities of both molecules show a clear resemblance, the intensities of the phenyl substitutes will sometimes decrease. On the other side, the odor tenacity (long-lasting-ness) of the phenyl derivatives is greater, and their substantivities are better. Several of these phenyl substitutes are commercially available. There is room for a lot more substitutes of monoterpenoids, for instance with: nerol/geraniol (esters), neryl/geranyl hemi-acetals, neric/geranic acid (esters), neryl/geranyl acetone, linalyl esters and hemi-acetals, citronellyl derivatives (see neryl/geranyl). Examples of commercially available aroma chemicals in which the isobutenyl part is substituted by a phenyl part are shown in T-1.

Substitution of Isoamyl by Cyclohexyl in Some Aroma Chemicals

The isoamyl group is a natural degradation product from leucine and often

Isoteric and iso-electronic molecular structures with similar odor qualities **F-2**



spicy (bitter almond)

freshe floral (lavender)

floral (rose)

citrusy (lemon)

fruity, floral (rose)

occurs in natural isolates, mostly as an ester. The lower aliphatic isoamyl esters may have strong fruity odors. A disadvantage of the application of these esters, however, is that they are too volatile and can rather easily soaponify. One may substitute the isoamyl group with a cyclohexyl group without disturbing the odor character to any great extent. Some examples of this substitution can be found in the odors of cyclohexyl salicylate, cyclohexyl phenethyl ether and allyl cyclohexyloxyacetate.

In T-2, the commercially available isoamyl and cyclohexyl esters are shown; there is still room for more of the latter.

T-3 shows examples of commercially available aroma chemicals in which the isopentyl part is substituted by a cyclohexyl part. Substitution of certain groups in molecules with more or less the same profile (shape, volume) and reminiscent odor characteristics are examples of isosteric molecules, with similar olfactive properties.

Substitution of Functional Groups

More than 95 percent of the commercially available fragrance and flavor chemicals contain one or more functional groups. One may question whether a functional group is necessary for the odor of a compound. No, it is not, because alkanes and benzenoid hydrocarbons sometimes have very pronounced odors. With this in mind, we wondered whether a trained observer was able to recognize an odorant by its functional group. Therefore we tested 100 aliphatic (normal C-3 to C-15) compounds with and without functional groups. Seven odor-trained chemists were used. Each observer received known standards with eight carbon atoms and 13 different functional groups (e.g. octane, octanol, octanal, octanoic acid, hexyl acetate, octanethiol, octylamine, etc.). The observers received all samples under codes; after smelling and comparing samples with the standards, each had to write the general chemical name (e.g. this is an alkane, alkcohol or thiol).

The results of the 706 tests were:

- 58 percent of the identifications were right, and 42 percent wrong;
- of the C-3 to C-6 compounds studied, over 80 percent were identified based on their functional groups;
- of the C-7 to C-10 compounds studied, over 80 percent of the aldehydes, alcohols and thiols were correctly identified; of the other funtctional group compounds, more than 50 percent were incorrectly identified;
- of the C-11 to C-15 compounds studied, only the thiols could be identified correctly; and of the other functional groups, 50-100 percent were incorrectly recognized.

The results with the methyl ketones and acetates are shown in T-4.

The methyl ketones C-7 to C-10 and the esters C-3 to C-10 were identified by their fruity odor character. The C-11 to C-15 compounds (methyl ketones, esters and alcohols) were often incorrectly identified because of their fatty odor characteristics.

From this experiment it seems likely that experienced observers, via odor perception, can substitute certain functional groups (ketones) with others (esters), even with the use of odor standards .

The same holds true for other functional groups, such as substitution of:

- aldehyde by nitrile in monoterpenoid and benzoid compounds;
- aldehyde by nitro in benzenoid compounds;
- *cis*-olefine by sulfur in straight-chain aliphatic compounds;
- chloro by methyl in aliphatic and benzoid esters;
- and allyl and geminal dimethyl by cyclopropyl in damasc(en)nones and ionones.

Some examples of replacement functional groups in odorants with the maintenance of the more or less

Commercial aroma chemicals with phenyl by isobutenyl substitution T-1

Original Aroma Chemical	Substituted Aroma (Chemical Identity)	Commercial Name Chemical	Odor Description (Supplier)
6-methyl-5-hepten-2-ol	4-phenylbutan-2-ol carbinol	methyl phenethyl	slightly floral, rose-like, sweet aromatic
citronellol (3,7-dimethyloct-6-enol)	3-methyl-phenylpentan-1-ol	Mefrosol (Quest) Phenoxanol (IFF) Phenylhexanol (Firmenich)	diffusive, fresh floral, rose absolute type
citronellal (3,7-dimethyloct-6-enal)	3-methyl-5-phenylpentanal	Mefranal (Quest)	green aldehydic
citronellylnitrile (3,7-dimethyloct-6-enenitrile)	3-methyl-5-phenyl-pentanenitrile	Hydrocitronitril (H&R) Citralis Nitrile (IFF)	citrusy, lime, fresh
geranylnitrile (3,7-dimethyl-2,6-octadienenitrile)	3-methyl-5-methyl-pent-2-enenitrile	Citronitrile (Haarmann & Reimer)	fresh citrusy, lemon like, somewhat aromatic-balsamic notes

Commercially available isoamyl and cyclohexyl esters* T-2

No.	Ester/Acid Part	Ester/Alcohol Part		No.	Ester/Acid Part	Ester/Alcohol Part	
		Isoamyl	Cyclohexyl			Isoamyl	Cyclohexyl
1.	acetate	+	+	19.	isobutyrate	+	+
2.	acetoacetate	+	-	20.	isovalerate	+	+
3.	angelate	+	-	21.	lactate	+	-
4.	anthranilate	-	+	22.	laurate	+	-
5.	benzoate	+	-	23.	2-methylbutanoate	+	-
6.	butyrate	+	+	24.	nonanoate	+	-
7.	cinnamate	+	+	25.	octanoate	+	-
8.	crotonate	+	+	26.	phenylacetate	+	+
9.	cyclopentenylacetate	-	+	27.	3-phenylpropionate	+	-
10.	decanoate	+	-	28.	propionate	+	+
11.	eugenyl	+	-	29.	pyruvate	+	-
12.	formate	+	+	30.	salicylate	+	+
13.	4-(2-furan)butyrate	+	-	31.	senecioate	+	-
14.	3-(2-furan)propionate	+	-	32.	3-(methylthio)propionate	+	-
15.	geranate	+	-	33.	tiglate	+	-
16.	heptanoate	+	-	34.	undecylenate	+	-
17.	heptinecarbonate	+	-	35.	valerate	+	-
18.	hexanoate	+	+		total number	33	13

*source: Allured's 2002 Flavor and Fragrance Materials

Commercial aroma chemicals with isopentyl by cyclohexyl substitution

T-3

Original Aroma Chemical and Chemical Identity (Commercial Name and Supplier)	Substituted Aroma Chemical	Commercial Name and Supplier	Odor Description
Isopentyl salicylate /3-Methylbutyl 2-hydroxybenzoate (Isoamyl salicylate)	Cyclohexyl salicylate	Cyclohexylsalicylat (Cognis)	sweet aromatic-floral, somewhat medicinal-phenolic
Allyl isopentoxyacetate /Prop-2-enyl-1 6-Methyl-3-oxaheptanoate (A.I.A.A.-Inoue) (Allonate-Quest) (Allyfate, Quest) (Allyl amyl glycolate, IFF) (Galballynate, Bell Aromatics) (Isoamylix, Charabot) (Isogalbanate, Dragoco) (Pentyrate, Sensient)	Allyl cylohexoxyacetate	Allyvert (Quest) Cyclogalbanat (Dragoco) Cyclogabaniff (IFF) Hexylix (Charabot) Isoananat (Haarmann & Reimer)	green, fruity, herbal, reminiscent of galbanum, pineapple connotation
Isopentyl phenylethyl ether /2-Isopentoxy-1-phenylethane (Anther, Quest) (Iphaneine, IFF) (Phenylethyl isoamyl ether, Toyotama) (Treflon, Takasago)	Cyclohexyl phenylethyl ether	Phenafleur (IFF)	floral note with hyacinth associations

Odor tests with aliphatic compounds: how seven experienced test subjects identified aliphatic methyl ketones and acetates of their functional groups

T-4

Compound	Number of Compounds	Number of Tests	Identified		Most frequent kind of mistake
			Right	Wrong	
methyl ketone (C3-C6)	3	21	76	24	spread
idem (C7-C10)	3	26	46	54	ester (50 percent)
idem (C11-C15)	3	21	0	100	alcohols (62 percent)
esters (C3-C6)	7	52	58	42	methyl ketones (25 percent)
idem (C7-C10)	8	51	80	20	spread
idem (C11-C15)	9	56	29	71	alcohols (29 percent)

similar odor character are shown in T-5. From the data provided, it is clear that sometimes functional groups can be replaced by others without a big change in the odor character. Substitution of functional groups in molecules with more or less the same electronical charge distribution and reminiscent odor characteristics are examples of iso-electronic molecules with similar olfactive properties.

The straight-chain aliphatic aldehydes octanal and decanal are, organoleptically, the character-impact compounds of orange peel oil, and could have much wider applications possibilities in perfume compounds. In fact, they are used in alcoholic perfumery in several luxury perfumes — for instance, Chanel No. 5. The application of these aldehydes in functional perfumery (soap, detergents and other houseproducts), however, has severe limitations because of the chemical stability of the aldehyde function (oxidation, condensation). Even in alcoholic perfumery, the aldehydes will form hemiacetals. Chemists working on structure-odor relationships will need to modify the functional aldehyde group. Such chemists have several tools at their disposal:

Examples of substitution of functional groups with same odor character T-5

Original Functional Group	Example Aroma Chemical	Substituted Functional Group	Substituted Aroma Chemical	Odor Description
aldehyde	citral	nitrile	geranylnitrile	citrusy, lemon-like
aldehyde	benzaldehyde	nitro	nitrobenzene	aromatic, spicy, bitter almond-like
acetate	isopentyl acetate	methyl ketone	5-methyl-heptan-2-one	fruity, banana-like
(Z)-ethylene	(Z)-hex-3-en-1-ol	sulfur (acetate)	3-thiapentan-1-ol (acetate)	green, freshly-mown grass, slightly sulfurous
chloro	(trichloromethyl)-benzyl acetate	methyl	trimethylmethyl-benzyl acetate	floral, rose-like
nitro	musk ambrette	acetyl	acetyl musk ambrette	musky, erogenic
gem.dimethyl	damasc(en)none)	cyclopropyl	damasc(en)one derivative	floral-fruity, rose- and rum-like
allyl/propenyl	(methyl)ionones	cyclopropyl	(methyl)ionone derivatives	floral-fruity, orris- and strawberry-like

- substitution of the aldehyde function by a chemically more stable group, such as a nitrile, acetyl or oxim;
- preparing of a vinyl ether of the aldehyde to give slow release of the aldehyde in acidic media;
- making an acetal of a lower alcohol with the same target;
- formation an equilibrium in a Schiff base with methyl anthranilate.

Molecular Parameters[15,19]

Various molecular parameters have been mentioned in the study of structure-activity relationships, particularly in the investigation of quantitative structure-activity relationships (QSAR) in pharmacochemistry for the development of new drugs. The Hansch approach has been widely accepted and recognized as a versatile way to understand drug action by analyzing structure-activity relationships in various biological systems. This approach assumes that the physicochemical factors governing the transport and drug-receptor interaction can be divided into hydrophobic, electronic and steric parameters. The hydrophobic character is often measured by the octanol/water partition coefficient. The general equation is: log (activity) - f (hydrophobic parameter) + f (electronic parameter) + f (steric parameter) + constant. The hydrophobic character is often measured by the octanol/water partition coefficient. The electronic parameter, for instance, can be: dipole moment, molar refractivity, dispersion forces (dipole bonding), molecular electrostatic potential, Hammett constant (degree of electronic release), highest/lowest (un)occupied molecular orbitals (HOMO - LUMO) and charge density. The steric parameter can be molecular volume, size and shape: Taft's steric constant, Charton parameter (related to Taft's). Further physicochemical parameters in structure activity studies can be: volatility and solubility.

Conclusions

A review has been given of published structure-odor relationships. All of these relationships possess valuable aspects, but most of the theoretical concepts are not practiced. Two main features — electronicity (electronic charge distribution over a molecule) and stereocity (volume, shape and profile of a molecule)—can qualitatively describe the molecular structures of odorant molecules. Odorant molecules with similar electronic and steric structures can reveal similar odor qualities. Sometimes chemical functional groups (aldehyde-nitrile-nitro, acetyl-acetate) with similar electronicity can be replaced by each other in odorants without disturbing the odor quality to a great extent. The same holds true for the substitution of sterical parts of the odoriferous molecule (phenyl-isobutenyl, cyclohexyl-isoamyl, sulfur-ethenyl, chloro-methyl), which determines stereocity.

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