Isomers and odor or nose as stereochemist

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Introducing

Smell is one of the most important senses. Originally, it was used for human hazard warning. Normally, we do not realize that the organ, which is using for smelling is also extremely sensitive analytical “machine” [1]. Actually, there are no two different structures of molecules, which would not be able to distinguish by the nose. It detects even small amounts of impurities in the sample, and most importantly, does it better than any analytical engine. Thanks to our olfactory receptors which are sensitive to the shape of the molecule, we are able to identify even small nuances related to aroma. Studies on the synthesis of new fragrant substances have shown that introducing changes in the spatial structure of the molecule can also affect the osmotic or aromatic properties of compound. Even small modifications of the structure may affect the spatial shape of the particles and therefore on adjust way to the receptor and how to connect to it. Previous studies have shown that stereochemical factors most affecting the flavor are – the configuration of the double bond and the configuration of chiral centers [2]. In this paper, we show the differences and similarities in fragrance between stereoisomers or spatial isomers. The pair of isomers have different smell and the intensity but also those where the only one change will trait such as intensity or fragrance notes.

The physical properties of aromatic compounds

Discussing the fragrances should be characterized some general features of the molecule. First of all, its molecular weight should be within the range of from 80 to 300u. The upper limit defines in turn a compound having a molecular weight 294u, or 13-methoxy-8ct, 13,13,20-diepoxy-14,15,16-trisnorlabdan (C18H30O3) (1) with an odor of ambergris.

\[ \text{Chemical structure of ambergris (1)} \]

In the other hand, one of the lightest compounds having aromatic properties are: H$_2$S with weight 34u and odor of rotten eggs and NH$_3$ (14u) of its characteristic odor [3-5]. Odorant molecule should also have a low polarity, surface activity, poor solubility in water and have a high lipophilicity and high vapor pressure. Importance is also the number and the type of functional groups (osmophores), but also hetero atoms such as nitrogen or sulfur, which are very important factors that affect the smell. An example of a compound containing in its structure only one osmophore – hydroxyl group is terpinen-4-ol (2) used in the creating compositions of the perfume with lavender and tea notes [6]. It is characterized by its spicy odor reminiscent of nutmeg, woody-earthy floral with lilac notes. There are other compounds which molecules have a greater number of osmophoric groups. Vanillin (3) with the scent of wood and vanilla contains in its structure three functional groups. Other compounds containing three osmophoric groups are synthetic nitro musk of scent of musk. Representative of this group is, discovered in 1894 by Albert Baur, musk ketone (4) [7].

The aromatic analogues of santalol

Christian Chapuis described a similar situation obtained by the santalol analogues (8) [10]. These compounds have surprisingly different properties than the original fragrance and osmophoric relationship between the properties and configuration of the double bond in the chain was even more noticeable (Tab. 1).

The presence osmophoric groups is not necessary for interesting smell of molecule. A suitable example is the diphenylmethane (5) with an odor like geranium leaves, which has no functional groups [2, 8].

**Table 1**

<table>
<thead>
<tr>
<th>R</th>
<th>Configuration</th>
<th>Odor</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>(R, E):(+)-9</td>
<td>scent of sandalwood</td>
<td>(R, Z):(+)-12</td>
<td>green tomato, fresh</td>
</tr>
<tr>
<td>Et</td>
<td>(R, E):(-)-10</td>
<td>scent of sandalwood, wood</td>
<td>(R, Z):(-)-13</td>
<td>not wood, butyric</td>
</tr>
<tr>
<td>Pr</td>
<td>(R, E):(+)-11</td>
<td>wood, sandalwood</td>
<td>(R, Z):(-)-14</td>
<td>green, fuzzy fruit, wood</td>
</tr>
</tbody>
</table>

Effect of the configuration of the double bond of the smell

Configurational isomers (E) and (Z) have usually very different sensory profile. Generally, it is considered that (Z)-isomers are more pleasant smell and are more “natural” than (E). The relationship of this type occurs in the case of isomers hept-4-enal, where the molecule of the (Z) has a pleasant odor cream-buttery and the other isomer is characterized by an aggressive smell of putty with green note [6]. However, there are many examples representing an exemption from this rule.

Synthesized by Wawrzenczyk et al. in nineties non-naturally occurring isomers (E) and (Z) 3,7-dimethyloookt-4-en-1-ol differ in both the intensity and the nature of the odor. (E)-3,7-dimethyloookt-4-en-1-ol (6) has an intense, pleasant floral scent with a hint of rose, while the (Z) isomer (7) is less intense, even pleasant, but with a distinct odor mushroom and a hint of vegetable [9].

**Table 2**

<table>
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Christian Chapuis described a similar situation obtained by the santalol analogues (8) [10]. These compounds have surprisingly different properties than the original fragrance and osmophoric relationship between the properties and configuration of the double bond in the chain was even more noticeable (Tab. 1).
A special case of stereoisomerism configuration is different arrangement of the substituents relative to the ring plane. This type of pairs of diastereoisomers tend to have different odors. An example is the cis isomer of Galaxolid® (23) with a pleasant, musky scent and fruity smelling of compound 24. In addition, the smell of the trans isomer is almost 700 times weaker than the cis [14].

Another pair of isomers – bicyclic ethers – have also different smell. Smell of ether 25 is described as camphor, charcoal with a hint of animal is nothing like floral-lily of the valley floral, green-balsamic aroma with a hint of wood ether 26 [15].

One of the most frequently used compounds for the creation of notes rose is a rose oxide. Two isomers (2S,4R)-27 ans (2R,4S)-28 were discovered in rose and geranium oil.

Use of all fragrance isomers became possible only after the development of asymmetric synthesis procedure, using (–)-citronellol [16÷18]. The characteristics of odor and configurations of rose oxide diastereoisomers are shown in Table 2.

### Table 2

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<th>Compound</th>
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<tr>
<td>(2S, 4R)-27</td>
<td>Floral-green, clean, rose, green, strong</td>
</tr>
<tr>
<td>(2R, 4R)-28</td>
<td>Floral-green, green, herbal, minty, fruity</td>
</tr>
<tr>
<td>(2R, 4S)-29</td>
<td>Herbal-green-floral, smell of hay, green, earthy</td>
</tr>
<tr>
<td>(2S, 4S)-30</td>
<td>Herbal-green-floral, fruity, herbal rose, citrus (bitter rind)</td>
</tr>
</tbody>
</table>

The two pairs of rose oxide diastereoisomers do not differ in the general description of the odor – (2S, 4R)-27 and (2R, 4R)-28 green-floral fragrance, and (2R, 4S)-28 and (2S, 4S)-29 herbal-green-floral. However, the characteristics of the fragrance notes are not so similar. In first pair odor changes from rose-green to green, herbal, mint-fruit in the second difference is even more evident: note changes from green-earthy to fruit, herbal-rose and citrus (bitter rind) [19].

Furanoid oxides of linalool were isolated in 1908 from essential plant Bussera sp Aniba roseodora. However, Felix determined their structure in the sixties of the last century [20]. Odor pairs of isomers shown below is the same – deciduous and earthy, and the difference is only in its intensity. Odor isomer (2R,5S)-31 is much stronger than the odor of (2R,5R)-33 [21].

### Enantiomers

One of the most important factors affecting both the intensity and the type of odor is the configuration of chiral centers in the molecule. Examples include isomers of borneol. In 1874 appeared the note on the different fragrance properties of the enantiomers. The study compared two different essential oils that differ in odor. Drynobalanops aromatica oil was weak camphor, pepper unpleasant odor and oil Blumea balsamifera camphoric-turpentine. After a series of investigations, it turned out that, in the first of the oils was a (1R, 2S, 4R)-(+) -borneol (33), while the second (1S, 2R, 4S)-(-)-borneol (34) [4]. In 1961 Ohloff [22], published a study on the perception of enantioselective chiral fragrances [18].
A difference in the fragrances of the enantiomeric pair is well shown in case of a pair of biodegradable products of α-isomethylionons. Smell of (S)-enantiomer (35) is described as a strong floral-fruity with a hint of iris, while (R)-isomer (36) as wood and animal and less intense [23].

Another compound is limonene – unsaturated hydrocarbon monoterpenic found in many fragrance compositions and food flavorings.

The isomer R-+(38) has a citrus scent with a hint of orange. It is a major component of the essential oils from the peel of citrus fruits where its content in essential even exceed 90%. However, S-(−)-(37) isomer has a pungent odor similar to turpentine with a hint of lemon. It was found, inter alia, in essential oils of Mentha family of plants and conifers [8, 18].

Due to its relatively interesting olfactory properties racemic Undecavertol® of Givaudan is used quite often for creating rose, fruit-pear notes. In the literature, the fragrance is described as strong a green-floral character, naturally fresh, fruity with a hint of violet leaf and linden flowers.

The pure enantiomers of this compound have different osmophoric properties. (R)-+(39) is similar to the racemate smell floral, green, fresh violet leaves, but it is stronger and more green. Moreover, there is also present a cucumber note and Neofolione (methyl ester of non-2-enoic acid). Smell of (S)-(−)-(40) is ten times weaker than the R-enantiomer; green fruit with a hint of balsam pinefru and also can feel the notes of tea [24].

Due to the characteristic note of fresh sea racemic Tropional® is used in many perfume compositions. Currently the industry produces 300–350 tons of this product. Its enantiomers fragrance characteristics often differ significantly. Smell isomer (S)-41 is described as a green floral with hints of the sea, and ozone similar to salt water, with a hint of sweet fruit and cumic. The compound (R)-42 has a floral scent, like the cyclamen and lily of the valley, with an aldehyde and a sweet, fruity-citrus note. Furthermore, these compounds differ in intensity – (S)-enantiomer is about five times more potent than (R) [25, 26].

Synthesized by Dams enantiomeric esters of p-menthene system have very similar characteristics perfumes. Both compounds are characterized by fruit and pear scent, and the only difference is due to the presence of woody notes in the (S)-44 enantiomer [27].

Also muscone enantiomers (45 and 46) have the same smell of musk. The only difference is the intensity of the odor. Detection threshold (−)-muscone (45) is five times lower than the (+)-isomer (46) [14, 18, 28].

A similar relationship can be observed in the case of Lilial® enantiomers (47). Both compounds have a fresh floral, lily of the valley like the smell with hints of lime and cyclamen, but the smell of isomer R-(−) is more intensive [5, 29].

Very interesting is the smell difference between enantiomers of unsaturated alcohol (49) and its silicon analogue (50). Both enantiomers of the alcohol (49) have a floral smell, but (−)-enantiomer is less intense. However, silicon analogues are completely different smell and intensity. (+)-Enantiomer (50) has a mushroom and earthy aroma and flavor (−) isomer is a floral, slightly rose [25, 30].

Summary

Observations of the world around us show that we like to surround themselves with scented objects. We also like to smell nice and actually cannot imagine life without smell. As a chiral substance, composed
of molecules with a specific configuration we can distinguish chiral objects, including through interactions between the fragrant molecules and receptors, we can distinguish between them by smell. For this reason, further studies of biological properties of stereo isomers are important. It should be noted that reliable data could be collected only in the case of compounds of very high purity. Therefore, no one should be surprised requirements for the development of stereoselective methods of preparation and separation of isomers.

Literature


Translation into English by the Author

Dr. Katarzyna WINSKA is a graduate of the Faculty of Chemistry, Technical University of Wroclaw in 1999. Doctor of Chemical Sciences was obtained in 2008. In 2011, she received the award in the „Inventor 2011” organized by Polish Federation Of Engineering Associations - NOT, the Patent Office RP, the Association of Polish Inventors and Innovators and the editors of „Technical Review”. She is currently an assistant professor in the Department of Chemistry at the Faculty of Food Sciences, University of Life Sciences in Wroclaw. Specialty - organic synthesis, chemical fragrance compounds, biocatalysis . She is co-author of 16 scientific papers, 31 posters at national and international conferences, about 50 patents.

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