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Structure-Activity-Relationships of Some *exo*-Isocamphanylcyclohexanols. Conformational Calculations on Sandalwood Odour IX[1]

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Summary. The odour differences of various *exo*-isocamphanylcyclohexanols are explained by molecular shape comparison. A partial matching of the molecular surfaces is used to evaluate necessary structural conditions for the Sandalwood scent.

Keywords. Molecular shape, molecular surface comparison; *Van der Waals* surface; *Connolly* surface; Computer aided fragrance design, sandalwood odour, *exo*-isocamphanylcyclohexanol.

Struktur-Aktivitäts-Beziehungen einiger Exo-Isocamphanylcyclohexanole. Konformationsrechnungen an Sandelholzriechstoffen IX[1]

Zusammenfassung. Die Geruchsunterschiede mehrerer *exo*-Isocamphanylcyclohexanole werden durch den Vergleich der Molekülform erklärt. Mittels einer teilweisen Anpassung der molekularen Oberflächen werden die notwendigen strukturellen Bedingungen für den Sandelholzgeruch bestimmt.

Introduction

Exo-Isocamphanylcyclohexanols were synthesized from camphor and phenol followed by catalytic hydrogenation [2]. The aim of the synthesis is the preparation of compounds with Sandalwood odour. The condensation reaction leads to various geometrical isomers concerning the position of the hydroxyl group at the cyclohexane ring. It has been pointed out that these isomers behave quite differently with respect to their odour impression [3]. In Table 1 all isomers of *exo*-isocamphanylcyclohexanols are listed together with the corresponding fragrance activity.

As shown in the table, only two of the isomers, namely **3a** and **5a**, possess a pronounced Sandalwood odour, two isomers, **5e** and **4a**, resemble to that fragrance, whereas in all other compounds this activity is lacking [3]. Some ideas have been proposed for an explanation of the differences of the fragrance [4], and in this paper we present the results of the application of a more subtile method of the comparison of molecular shapes.

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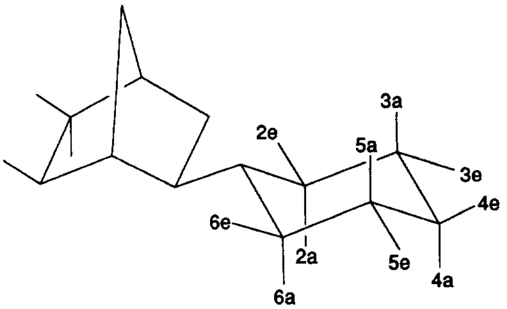
[1] For part VIII see Ref. [1]

Table 1. Fragrance of the various *exo*-isocamphanyl-cyclohexanols

Isomer	Fragrance
2a	no Sandalwood odour
2e	no Sandalwood odour
3a	***strong Sandalwood odour***
3e	no Sandalwood odour
4a	*resemblance to Sandalwood odour*
4e	no Sandalwood odour
5a	***strong Sandalwood odour***
5e	*resemblance to Sandalwood odour*
6a	no Sandalwood odour
6e	no Sandalwood odour



Experimental

The method used has been described elsewhere extensively [5, 6]. The calculation of the molecular surfaces is based on the superposition of energetically favourable conformations of the molecules with a standard (a rigid molecule with pure Sandalwood odour). The superposition itself is performed by evaluation of the largest common volume of both molecules, but with respect to the orientation of the functional groups, which have to be superimposed as accurate as possible. The reason for such a restriction is the fact that the common subunit of all molecules under investigation, which is postulated to be important for the association at a receptor protein, should include the functional group, *e.g.* a hydrogen bond. The superimposed molecules are analyzed in terms of the similarity of the molecular surfaces. By means of a calculation of the intersection points of the individual surfaces with defined lines through the molecular center and by comparison of these intersection points of various molecules on one line a quantitative measure of the coincidence of the surfaces can be determined. The difference of the intersection points are summed up for small or no deviations in the range between -0.3 and $+0.3$ Å and for larger surface deviations higher than 0.7 Å. In the latter case the sum value is multiplied by the deviation distance. Additionally, the positive and negative sign of the deviations from the surface of the Sandalwood standard molecule has to be considered. A rough partition of the molecular surface into octants allows the analysis of different molecule parts. With an additional option of the program a matching of the total and partial molecular surface can be performed.

Results and Discussion

For the comparison of the *exo*-isocamphanylcyclohexanols, 8-*tert*-butyl-bicyclo-[4.4.0]decanol-1 [7] was selected as standard molecule, because it is a typical Sandalwood odour molecule with a rather rigid structure and exists only in a single conformation, if one neglects the rotation of the hydroxyl group, which seems reasonable for the present investigation.

Table 2 represents the quantitative description of the surface deviations between the standard and the various *exo*-isocamphanylcyclohexanols. Only the isomer **4e** is omitted because the superposition of that compound with the standard is not possible in a sensible way. Such a comparison of the total molecular surface shows no pronounced significance between Sandalwood odour molecules and the others. The percentage values of the deviations between -0.3– $+0.3$ Å are a little bit higher than for most of the other isomers. The positive deviations, which may hinder an efficient receptor reaction, are less, but the isomer **4a**, which only resembles to Sandalwood odour, shows better values in all other cases.

The comparison of the total molecular surface is therefore not significant enough to give a decisive picture of the contact regions. It is evident that only parts of the surface belong to the common structural subunit which is responsible for the selectivity of the Sandalwood fragrance.

One of the easiest possibilities of the investigation of parts of the molecular surfaces is to divide the space round the molecules into octants by planes defined by the axis of the *Cartesian* coordinate system. The numbering of the octants and the orientation of the standard molecule in the coordinate system is given in Fig. 1.

A matching procedure in the first octant, which is close to the hydroxyl group of the molecules, leads to a much clearer picture of the fragrance properties of the different isomers. The total surface coincidence of all isomers decreases, because

Table 2. Comparison of the total molecular surfaces of the *exo*-isocamphanylcyclohexanols with 8-*tert*-butylbicyclo[4.4.0]decanol-1 (standard molecule). The third column in the table represents small deviations of both molecular surfaces. The value is given in percentage of all intersection points (w_i). The second and forth column show larger deviations. The percentage values are multiplied in these cases by the square of the distance at one line to obtain a weighted quality of the size of the deviation ($w_i \cdot r_i$)

Isomer	< -0.7 Å	-0.3 Å–$+0.3$ Å	>0.7 Å
2a	3.47	50.0	6.39
2e	5.59	50.0	9.05
3a	***3.03***	***53.43***	***8.34***
3e	4.05	45.32	7.99
4a	*3.24*	*67.20*	*8.12*
5a	***4.15***	***51.72***	***9.43***
5e	*6.09*	*46.72*	*11.19*
6a	3.70	58.28	7.33
6e	8.35	50.94	14.28

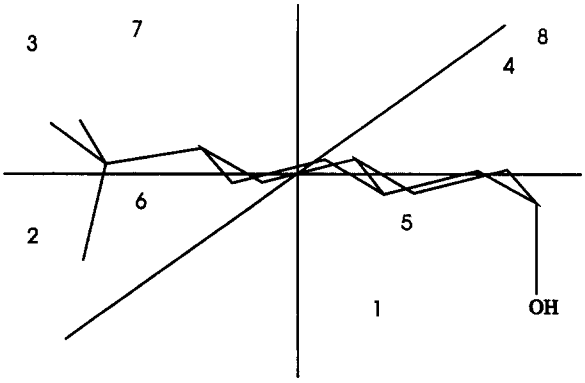


Fig. 1. Position of 8-*tert*-butylbicyclo[4.4.0]decanol-1 in the coordinate system together with the definition of octants

Table 3. Comparison of the second octant (*cf.* Fig. 1) of the molecular surfaces of the *exo*-isocamphanylcyclohexanols with 8-*tert*-butylbicyclo[4.4.0]decanol-1 (standard molecule), if a partial surface matching is performed in the first octant. The statistics of the surface regions is the same as in Table 2

Isomer	< -0.7 Å	-0.3 Å–$+0.3$ Å	>0.7 Å
2a	21.40	23.45	0.0
2e	1.58	41.98	26.10
3a	***1.58***	***61.73***	***3.95***
3e	42.95	37.03	10.93
4a	*0.0*	*32.09*	*30.42*
5a	***4.49***	***62.96***	***3.26***
5e	*25.01*	*28.39*	*17.66*
6a	3.26	55.56	20.81
6e	7.99	41.97	13.18

only a much smaller surface region is used for matching, but the values of the fragrance molecules **3a** and **5a** change only for 6%, whereas the change of compound **2a** is 12%. By comparison of the molecular surfaces in other octants a pronounced difference between the Sandalwood odour molecules and the others can be detected. Table 3 gives an interpretation of the surface statistics for octant number 2, which is also close to the hydrophobic center of the molecules.

The coincidence of compounds **3a** and **5a** with the standard molecule is significantly better than for the other isomers. 61.73 and 62.96 are the highest values for all isomers. The amount of coincidence is also high for compound **6a** (55.56%), but there exists a strong positive deviation for this compound (deviation value of 20.81). Not only the amount of surface dots with small deviations (third column in the table) is much higher for the fragrance molecules, also the positive deviations from the standard (forth column) are much less. It can be concluded therefore that the surface region around the hydroxyl group is of high importance for the association process

Table 4. Comparison of the fifth octant (*cf.* Fig. 1) of the molecular surfaces of the *exo*-isocamphanylcyclohexanols with 8-*tert*-butylbicyclo[4.4.0]decanol-1 (standard molecule), if a partial surface matching is performed in the first octant. The statistics of the surface regions is the same as in Table 2

Isomer	< −0.7 Å	−0.3 Å–+0.3 Å	>0.7 Å
2a	43.75	36.70	0.0
2e	74.46	15.18	0.0
3a	***22.41***	***46.83***	***2.07***
3e	33.57	27.87	0.0
4a	*4.90*	*82.28*	*2.43*
5a	***17.79***	***43.02***	***6.53***
5e	*65.18*	*30.38*	*0.0*
6a	1.26	75.94	3.24
6e	6.69	63.29	8.40

at the receptor site. This fact seems to be reasonable, because an association at a peptide or a protein may be performed via an hydrogen bridge. In addition, this result is in agreement with investigations on other Sandalwood compounds [8, 9]. For the search of further important surface regions the comparisons in other octants have to be performed. In octant number five, where the hydrophilic residue of the molecule is located, also a rather good coincidence of the fragrance molecules can be observed (Table 4).

Compounds **3a** and **5a** again show a good coincidence of the surfaces, but also other isomers behave quite similar (*e.g.* **6a**). As these non fragrant molecules show no good comparison in the second octant, the coincidence in the fifth octant seems to be a necessary, but not sufficient condition for the surface structure.

Some parts of the molecular surface must have a certain, and sometimes a rather precise shape for selectivity and the sensitivity of a biological effect, in the presented case, the Sandalwood fragrance. This "necessary condition" occurs from the interaction from molecule parts with the receptor surface or the interaction of functional groups with the corresponding receptor subunits. In various isomers of the *exo*-isocamphanylcyclohexanols, the surface region around the hydroxyl group and a part of the hydrophobic group (in octant 5) seems to be such a "necessary condition". Other parts of the molecular surface have more freedom of surface variations, some "weaker conditions" have to be proposed in these cases. A "weaker condition" may be the fact that no too large bulky group is located at such a surface region.

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References

[1] Neumann A., Weiß P., Wolschann P. (1993) J. Molec. Struct. **296**: 145
[2] Demole E. (1964) Helv. Chim. Acta **47**: 319
[3] Demole E. (1969) Helv. Chim. Acta **52**: 2065
[4] Becker A., Buchbauer G., Winiwarter S., Wolschann P. (1990) J. Ess. Oil Res. **2**: 221
[5] Buchbauer G., Winiwarter S., Wolschann P. (1992) J. Comp. Aided Molec. Design **6**: 583
[6] Becker A., Buchbauer G., Winiwarter S., Wolschann P. (1992) Monatsh. Chem. **123**: 405
[7] Witteveen J. G., Van der Weerdt A. J. A. (1987) Recl. Trav. Chim. Pays-Bas **106**: 29
[8] Buchbauer G., Stock S., Weiß P., Winiwarter S., Wolschann P. (1992) Z. Naturforsch. **47b**: 1759
[9] Buchbauer G., Leonhardsberger K., Winiwarter S., Wolschann P. (1992) Helv. Chim. Acta **75**: 174

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