

## Surface comparisons of some odour molecules: Conformational calculations on sandalwood odour V

Gerhard Buchbauer<sup>a</sup>, Susanne Winiwarter<sup>a</sup> and Peter Wolschann<sup>b,\*</sup>

<sup>a</sup>Institut für Pharmazeutische Chemie, and <sup>b</sup>Institut für Theoretische Chemie und Strahlenchemie der Universität Wien,  
Währingerstraße 10 and 38, A-1090 Wien, Austria

Received 24 February 1992

Accepted 16 July 1992

*Key words:* Molecular shape; Molecular surface comparison; Van der Waals surface; Computer-aided fragrance design; Sandalwood odour

---

### SUMMARY

Molecular surface comparison seems to be a very suitable tool for the investigation of small differences between biologically active and inactive compounds of the same structural type. A fast method for such comparisons, based on volume matching followed by the estimation of comparable surface dots, is presented and applied on a few selected sandalwood odour molecules.

---

### INTRODUCTION

The olfactory system is a human sense which recognizes some volatile compounds in an extremely sensitive way and which discriminates a rather large number of different odour qualities [1–5]. Despite numerous efforts to elucidate the basis of odour perception, the concrete physicochemical mechanism, especially connected with the stereochemistry of the association process, is still unclear. Some molecular approaches have been followed to identify the structure of a possible receptor site; usually, a structural element common to a series of odour molecules with identical fragrance was looked for to estimate the complementary molecular contact surface [6]. There is no exactly defined correlation between odour quality and molecular properties for fragrance molecules, but it seems to be clear that some physicochemical parameters, such as vapour pressure, polarity and hydrophilicity, are important for the biological effect of such molecules. Additionally, the shapes of the molecular surfaces, together with their distinct electron distributions, are most important for a molecule's selectivity.

To obtain information about the receptors responsible for fragrance recognition, a series of

---

\* To whom correspondence should be addressed.

molecules with a typical sandalwood odour was analysed in order to look for the common structural subunit which could be responsible for the biological effect. The class of sandalwood odour molecules is well investigated [7–9]. More than 70 natural as well as synthetic molecules with that warm woody fragrance are known. Due to the relatively large differences in the molecular geometries within this class of compounds, an investigation of the structure–activity relationship promises interesting results. Sandalwood odour is also a very fascinating fragrance because of its likeness to androstenol-3, an odour compound of the human body, and to other scents such as musk and ambergris [10,11]. The idea that all molecules of these scents might interact with the same receptor is supported by the fact that the whole odour group tends to anosmia and dysosmia in a comparable manner. Interestingly, the fragrance of androstenol-3 is often described divergently in the literature [8,12,13] as sandalwood-like or urinous or resembling a musk scent.

For the investigation of the common structural elements in the group of sandalwood odour molecules, the different conformations of the respective molecules first had to be estimated by molecular mechanics calculations. Various matching routines, either considering several atoms of each molecule or the shape of the molecules by calculating their volume in common, were applied to achieve superposition of the studied molecules as accurately as possible. A simple and fast method was developed for a comparison of the molecular surfaces of the matched molecules. With a semi-quantitative procedure some numerical information can also be obtained about such surface differences between sandalwood odour molecules and molecules with similar structure but without that typical fragrance.

## METHOD OF CALCULATION

A prerequisite for surface comparisons is a complete conformational analysis of the compounds under investigation. The program package MOLBMEC [14], a molecular mechanics program based on Allinger's MM2 parameter set [15], was used for the calculation of all possible conformations of the molecules. The resulting coordinates were stored in a database together with information about their energies. For further investigations only conformations with energy differences of less than 5 kcal/mol from the total energy minimum were considered, as energetically unfavourable structures are not present in a thermodynamic equilibrium at room temperature, according to Boltzmann statistics. Such 'high energy' conformations cannot be responsible for an association of the molecule at a receptor site for energetical reasons, even if an exothermic association reaction is postulated.

In the next step, all appropriate conformations of the molecules were superimposed onto one standard molecule, using the matching routine GUDCON [1]. By selecting useful matching criteria for this superimposition, all molecules can be oriented alike, so that comparable surface regions of the respective structures are put into the same region of space.

As shown in the flow chart diagram (Fig. 1), the superposition of the molecules with the standard, a rather rigid molecule with the typical sandalwood odour, is started by matching several selected atoms. It seems reasonable to select atoms of the same functional group or with comparable electron density for this atom-matching routine. In the case of sandalwood odour molecules, the oxygen atom of the hydroxyl group and the adjectant carbon atom were chosen. As third atom, one atom of the bulky residue, which can be found in all molecules, was selected in respect to the general shape of the molecules. As it is rather difficult to determine a concrete atom within the

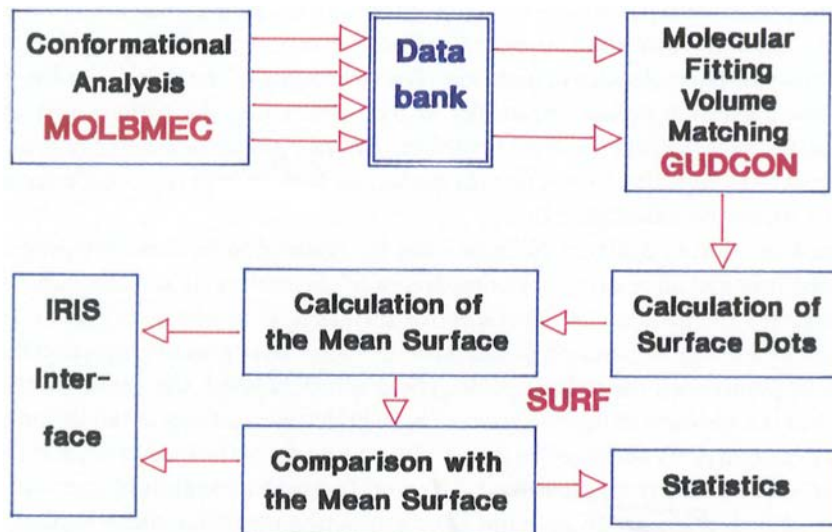


Fig. 1. Scheme of the procedure used to calculate the surface comparisons (referring to the program packages used).

group of rather similar atoms, special features of GUDCON had to be used. The program module selects from a set of given atoms that one atom which is closest to the atom of the standard. It is also possible to define a dummy atom as a centre of several real atoms of the molecule [1].

The matching procedure itself can be performed by using either a least-squares fit or the McLachlan algorithm [16]. The RMS (root-mean-square) value is taken as first criterion for the quality of the match. But as the RMS value is strongly dependent on the atoms used for the matching procedure and as it is therefore rather arbitrary about the molecular shapes as second criterion, the volume common to both the standard and the respective conformation was calculated as a per cent of the whole volume. To this end a mesh is constructed around the structures in question. Each point of this mesh represents the midpoint of a parallelepiped. The volume of the two structures as well as the volume common to both of them can thus be estimated easily by counting all the points of the mesh which are located inside one or the other molecule or within both of them. To obtain the total molecular volume, this number must be multiplied by the volume value for one parallelepiped. In the next step, the agreement between the two molecular shapes is improved by optimizing the volume in common. As before, it is only necessary to shift and to rotate the compared molecule with respect to the standard. With the help of a minimizing routine [17], using the simplex algorithm, a value for the common volume higher than the starting value is usually found. As volume-matching is rather time-consuming, it is therefore a useful strategy to start the calculations with atom-matching and to consider only those matched versions that already show a good volume agreement between the molecule and the standard. The less reliable atom-matching is therefore only a prestep for the more accurate volume-matching procedure.

For the conformations with the best volume agreement, a surface comparison was performed using the program module SURF. The aim of the method used by this module is to calculate surface dots, which are conveniently comparable to other surfaces. It is not so important to describe

the molecular surface by dots spread as evenly as possible, as it is in other surface calculations [18–22]. In the presented method lines are defined through the geometrical midpoint of the standard molecules. The surface dots are estimated as the intersection points of these lines with the Van der Waals surface of the molecules in question. The two angles of the polar coordinates,  $\Phi$  and  $\theta$ , are used. These angles are varied empirically in such a way that the surface dots are spread as evenly as possible over the total molecular surface. About 2000 surface dots are usually calculated, which seems to be sufficient to describe the molecular surface with reasonable accuracy, within the limit of an acceptable calculation time.

Dots of one line – but of different surfaces – can be assumed to be corresponding, as all molecules have been oriented alike earlier. A comparison of the molecular surfaces can now be easily made by measuring the distance of the respective surface dots of one line (Fig. 2). In Fig. 2 the green points represent the intersection points with the molecule drawn in green, and the red points the intersection points with the red molecule. The distance between the green point and the red point of one line is a measure of the deviation of both molecular surfaces in the region of the line.

The surface comparisons described in this study are usually performed in several steps. First, a ‘mean surface’ is computed from the surfaces of several active compounds by calculating the average values of all surface points on each line. The estimation of such a ‘mean surface’ has several advantages. As not only the mean value for each surface dot is calculated, but also the spread of the values, those surface regions of the active compounds that coincide or are similar can be easily found. Additionally, the comparison with the average of several molecular surfaces definitely gives more significant results with respect to the differences between active and inactive compounds than the comparison of only two individual surfaces. The surfaces of all molecules under investigation, active or inactive, are therefore compared to this ‘mean surface’.

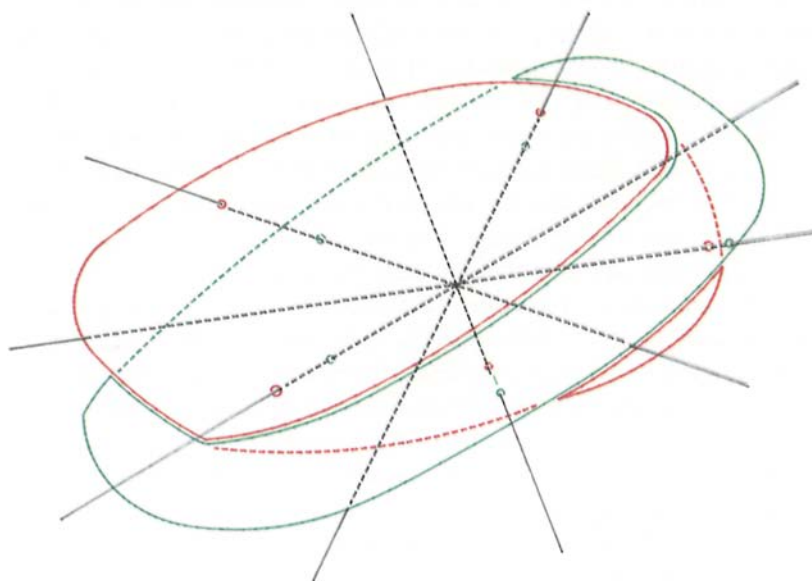


Fig. 2. Estimation and comparison of molecular surfaces.

The results of the surface comparison can be shown either in a graphical representation or as a table, in which all surface dots with a certain distance to the corresponding dots of the 'mean surface' are summarized. In the graphical representation, the parts with different deviations from the 'mean surface' are distinguished from each other by a special colour for such surface regions. The tables can be represented in another graph showing the distribution of the surface dot deviations for each molecule. For clearness, the deviations are reduced to three significant values. One of these values includes all surface dots which are close to the 'mean surface' (the distance to the corresponding average surface dot should be less than 0.3 Å). The other two values describe those surface parts that are far away from the 'mean surface'. For significance reasons it seems appropriate to consider the magnitude of the deviations also and not only the number of points which show a rather large deviation from the 'mean surface' (in this case, larger than 0.7 Å). Therefore, the deviation values were squared and then multiplied with the number of the corresponding dots.

The sign of the deviation of the individual surface from the 'mean surface' is also considered. The surface parts with a negative deviation from the 'mean surface' are distinguished from those with a positive deviation. 'Negative surface parts' are surface parts that are smaller than the 'mean surface'. In contrast to this, 'positive surface parts' are parts outside the mean surface, which indicates that the molecule is larger than the average in this surface part. Such positive deviations from the 'mean surface' seem to be especially important because a possible interaction between the compounds and a potential receptor might be prevented by steric hindrance, whereas negative surface parts only diminish the contact surface between molecule and receptor, which leads, of course, to a smaller association constant.

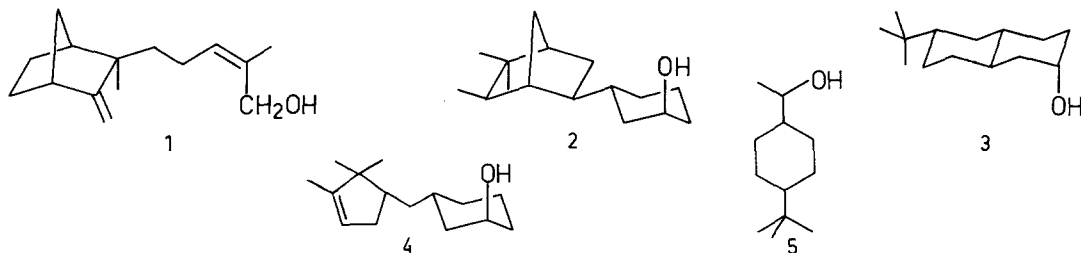
Additionally, following the chart diagram (Fig. 1), a graphical presentation of the mean surface can be performed on a graphical workstation, using the program package MOLCAD [23]. The standard deviation of each surface dot is projected onto the molecular surface in different colours. Such a visualization makes it possible to detect surface regions with a rather good agreement of individual surfaces. A similar presentation can be drawn for comparisons of other molecular surfaces with the 'mean surface'.

## SURFACE COMPARISONS OF SANDALWOOD ODOUR MOLECULES

The method described above was used to compare some sandalwood odour molecules of similar structure without this typical fragrance. The 'mean surface' was calculated for five fragrant compounds of different types (shown below).

As it can be easily seen, they all belong to very different groups of sandalwood odour molecules:

$\beta$ -Santalol (**1**), the main component of natural sandalwood oil, consists of a bicyclic ring system and a relatively flexible side chain with a hydroxyl group. Due to the possibility of the more-or-



less free rotation of four carbon-carbon single bonds, 81 conformations of the molecule have to be taken into account. The rotation of the hydroxyl group, which does not change the shape of the molecule very much, was neglected.

*Exo*-Isocamphanylcyclohexan-3-ol (**2**) [24,25] has a cyclohexane ring connected to a bicyclus. In this molecule, the number of possible conformation is drastically reduced compared to **1**, as only the rotation around the carbon-carbon single bond between both cyclic structures has to be considered. This leads to just three different conformations. The inversion of the cyclohexane ring causes only one additional conformation in the energetically suitable range.

In the case of *tert*-butylbicyclodecanol (**3**) [26] only one conformation has to be considered; the rotation of the *t*-butyl groups leads to identical structures.

Trimethylcyclopentenylmethylcyclohexan-3-ol (**4**) [27] is rather similar to **2**. Instead of the bicyclus, a substituted cyclopentenylmethyl residue is connected to the cyclohexane ring. Due to the free rotation of the two carbon-carbon single bonds, at least nine different conformations have to be taken into account, together with the different ring conformations.

The fifth compound, *cis*-1-hydroxyethyl-4-*tert*-butylcyclohexane (**5**) [28], belongs to the group of cyclohexane derivatives, which have already been studied by surface comparison methods [1].

Of the five mentioned substances, **3** shows the most rigid structure. Therefore, this molecule was selected as standard for the following calculations. Additionally, its fragrance is described to be clean and typically sandalwood-like [26].

Each of the considered molecules was superimposed on the standard molecule **3** in such a way that an identical orientation of the polar group, the carbinol group, was taken into account for both molecules. Atom-matching, as described earlier, followed by volume-matching was applied. The conformation of each molecule with the best agreement with the standard was selected for the following 'mean surface' computation.

Figure 3 shows one half (the front part) of the 'mean surface' calculated from the molecular surfaces of the five mentioned sandalwood odour compounds. Its colouring, showing more green and black parts than orange ones, indicates a rather good agreement of the surfaces of all five mole-

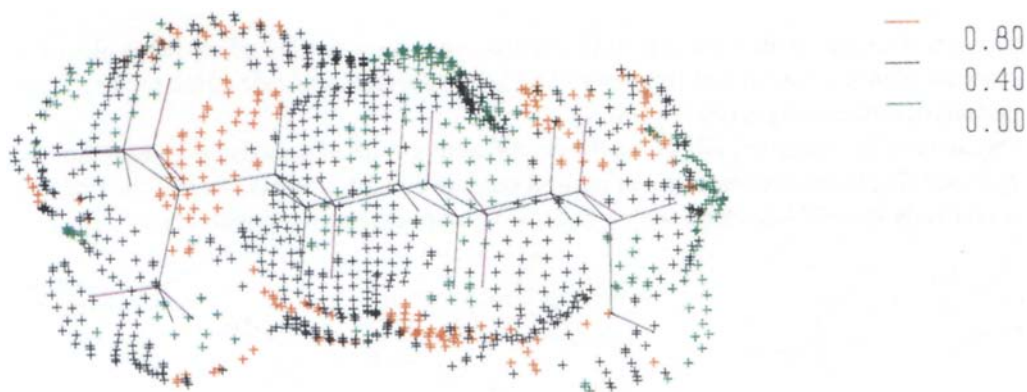


Fig. 3. 'Mean surface' calculations for compounds **1–5** (only the front part is shown). Colouring corresponds to the standard deviations.

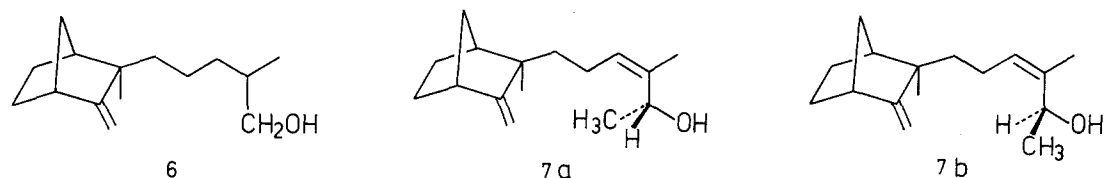
TABLE 1  
DEVIATIONS OF THE INDIVIDUAL SURFACES FROM THE MEAN SURFACE CALCULATED FROM 1-5

Compound	Weighted deviation (*d <sup>2</sup> ) -0.7 Å	% Deviation -0.3 - +0.3 Å	Weighted deviation (*d <sup>2</sup> ) 0.7 Å
<b>1</b>	34.47	34.79	16.38
<b>2</b>	6.83	33.14	15.53
<b>3</b>	12.64	42.87	11.39
<b>4</b>	16.76	38.34	13.67
<b>5</b>	35.53	30.81	17.74

cules. Green parts represent dots with a standard deviation of less than 0.4. Black points represent deviations up to 0.8, and orange dots characterize surface parts with a standard deviation larger than 0.8. This relatively good agreement of all five molecules is rather surprising as their structures seem to be very divergent. Obviously the chosen orientation, which took care of centres with comparable electron density within the respective molecules, was suitable for the superposition of the different parts of the molecules in comparable regions of space.

In the next step, the five molecules were also compared individually with the 'mean surface'. The calculated deviations were collected and summarized as described before. The results are given in Table 1. It can be stated that for all five molecules at least one third of the individual molecular surface is rather close to the 'mean surface', with deviations of less than 0.3 Å from it. There are only rather small surface parts with a deviation of more than 0.7 Å, either within or outside the 'mean surface'. Only for **1** and **5** is the value for the weighted deviation in the negative range higher than 30.

The same 'mean surface' was also compared with a few other similar active and inactive compounds. In this study, three derivatives of  $\beta$ -santalol were used (shown below).



$\beta$ -Santalol (**1**) and, according to [29], dihydro- $\beta$ -santalol (**6**) are components of East Indian sandalwood oil, but the concentration of the latter in the oil is lower than that of  $\beta$ -santalol. The odour of the side-chain saturated **6** is sandalwood-like, but of diminished intensity [30]. The partial saturation is of course the reason for a much larger number of energetically possible conformations for **6** than for **1**. One is tempted to believe that this fact alone would lead to a better agreement with the standard, as well as with the 'mean surface'. Considering the common volume as criterion for a good agreement, the value is higher for **6** than for **1** (see Table 2). But the agreement of the molecular surfaces seems to be better for  $\beta$ -santalol (see Tables 1 and 3), because in **1** the part of the surface with a positive deviation is definitely smaller. Still, the surface of **6** is rather close to the 'mean surface'; one third of it has a deviation of less than 0.3 Å.

The other two homologues of  $\beta$ -santalol used in this study are the two enantiomers **7a** and **7b**

TABLE 2  
AGREEMENT OF MOLECULAR VOLUME IN % OF WHOLE VOLUME AND ANGLE BETWEEN THE RESPECTIVE C-O AXES

Compounds	Common volume %	Angle °
<b>3-1</b>	58.70	14.61
<b>3-6</b>	60.83	13.30
<b>3-7a</b>	57.16	12.03
<b>3-7b</b>	56.58	6.44

(diagram 2). In comparison to **1** they possess one additional methyl group next to the hydroxyl group, which leads to another chiral centre within the molecule. As the synthesis led to a racemic mixture [31], both enantiomers had to be taken into account for the calculation. Although the common volume for both molecules is rather high (see Table 2), the molecular surfaces of **7a** and **7b** are distinctly different from the 'mean surface', as documented in Table 3.

In Table 2 the angle between the carbon-oxygen bonds of both molecules, which have been volume-matched, are also given. In all cases the angle is not greater than 15 degrees, which seems reasonable for an association, via a hydrogen bond, with the molecules at a receptor site.

The surface part which coincides to the 'mean surface' is less than 30%, whereas the values describing the surface deviations of more than 0.7 Å in both directions appear to be larger than 35 for **7a** as well as for **7b**.

A visualization of the comparison of the surfaces of **3** and **7a** with the 'mean surface' is given in Fig. 4. In the bar diagram (Fig. 4A), the percentage of the number of dots at a certain distance from the corresponding points of the 'mean surface' is correlated with the distances themselves. The distribution of the deviations is different for both compounds, and especially the rather high deviation values indicate a bulging of the surface of **7a** compared to that of the standard, which might sterically hinder an association at a possible receptor site. Another simplified presentation of weighted deviation values (also given in Table 3) is shown in Fig. 4B. Again, a larger positive deviation can be recognized.

From the diagrams and tables given above, a diminished surface similarity of **7a** and **7b** with respect to the standard can be deduced in comparison to other odourous compounds. The conclusion that both compounds show no sandalwood odour was confirmed by odour evaluation.

The procedure described in this paper is an easy and relatively fast method for the comparison of molecular surfaces, which is especially useful for the investigation of the fragrance-structure relationship of sandalwood odour molecules. The counting of the deviations of corresponding sur-

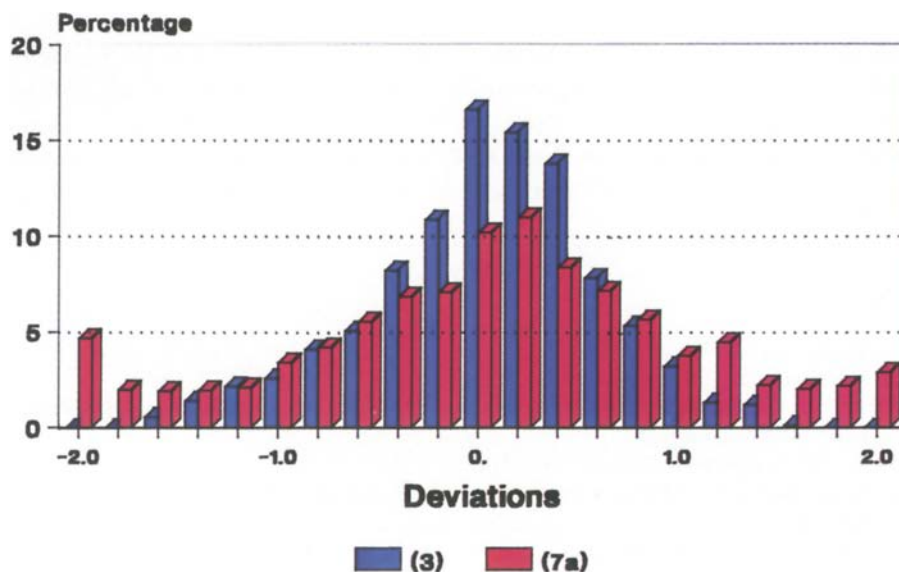
TABLE 3  
DEVIATIONS OF THE INDIVIDUAL SURFACES FROM THE MEAN SURFACE

Compound	Weighted deviation (*d <sup>2</sup> ) -0.7 Å	% Deviation -0.3 - +0.3 Å	Weighted deviation (*d <sup>2</sup> ) 0.7 Å
<b>6</b>	22.32	33.09	23.40
<b>7a</b>	43.27	28.28	42.37
<b>7b</b>	37.51	26.04	35.30



A

### Surface Comparison Deviations from the mean surface



B

### Surface Comparison Weighted deviations

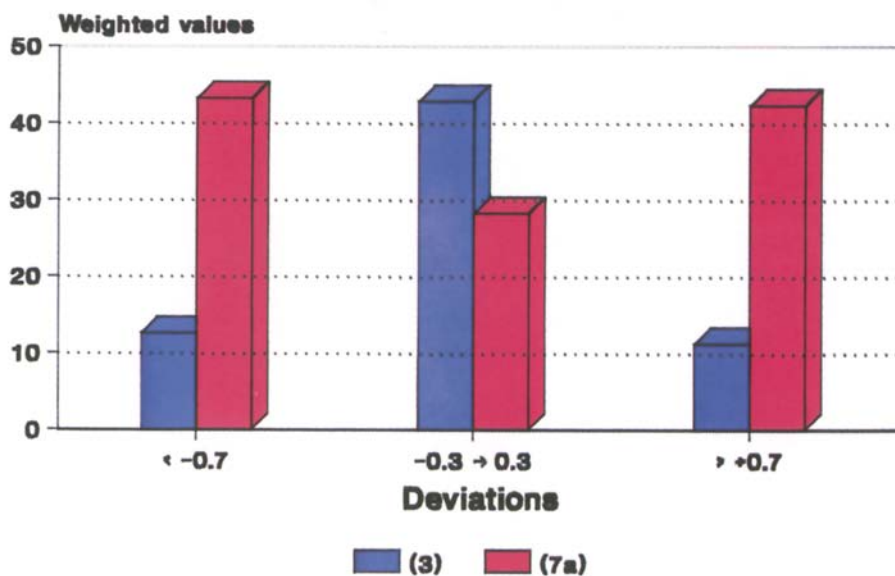


Fig. 4. Bar diagrams of the deviations of the individual surface dots of 3 and 7a with the 'mean surface' points (A). In (B) the reduced weighted values are given.

face points allows a quantitative description of the surface structure necessary for the biological effect.

## ACKNOWLEDGEMENTS

The authors are indebted to Prof. P. Schuster for helpful comments and the Fonds zur Förderung der Wissenschaftlichen Forschung for financial support (Projekt P7758) and for the disposal of a graphic workstation IRIS 3115 (Projekt P7533). We thank the Rechenzentrum der Universität Wien for computer time on the IBM 3090. We also gratefully acknowledge the friendly interest in our work by DRAGOCO-Vienna and the odour evaluation by the perfumers V. Hausmann and M. Watson.

## REFERENCES

- 1 Becker, A., Buchbauer, G., Winiwarter, S. and Wolschann, P., *Monatsh. Chem.*, 123 (1992) 405.
- 2 Ohloff, G., *Riechstoffe und Geruchssinn*, Springer-Verlag, Berlin-Heidelberg, 1990.
- 3 Theimer, E.T. (Ed.), *Fragrance Chemistry: The Science of the Sense of Smell*, Academic Press, New York, 1982.
- 4 Ohloff, G., *Experientia*, 42 (1986) 271.
- 5 Buchbauer, G., *Österr. Apotheker-Zeitung*, 35 (1981) 37.
- 6 Amore, J.E., In Theimer, E.T. (Ed.), *Fragrance Chemistry: The Science of the Sense of Smell*, Academic Press Inc., New York, 1982, p. 27.
- 7 Lancet, D. and Pace, U., *TIBS*, 12 (1987) 63.
- 8 Brunke, E.J. and Klein, E., In Theimer, E.T. (Ed.), *Fragrance Chemistry: The Science of the Sense of Smell*, Academic Press Inc., New York, 1982, p. 397.
- 9 Naipawer, R.E. In Lawrence, B.M., Mookherjee, B.D. and Willis, B.J. (Eds.), *Flavors and Fragrances: A World Perspective*. Proc. of the 10th Congr. of Ess. Oils, Frag. and Flavors, 1988, Elsevier, Amsterdam, 1988, p. 805.
- 10 Brunke, E.J. and Klein, E., In Mookherjee, B.D. and Mussinan, C.J. (Eds.), *Essential Oils*, Allured Publ. Corp., Wheaton, U.S.A., 1981, p. 83.
- 11 Beets, M.G.J., In Theimer, E.T. (Ed.), *Fragrance Chemistry: The Science of the Sense of Smell*, Academic Press, New York, 1982, p. 77.
- 12 Brunke, E.J., *Dragoco Reports*, 30 (1983) 27.
- 13 Stoddart, D.M., In Van Toller, S. and Dodd, G.H. (Eds.), *Perfumery: The Psychology and Biology of Fragrance*, Chapman and Hall, London-New York, 1988, p. 3.
- 14 Beyer, A., Wolschann, P., Becker, A. and Buchbauer, G., *J. Mol. Struct.*, 196 (1989) 371.
- 15 Allinger, N.L., *J. Amer. Chem. Soc.*, 99 (1977) 8127.
- 16 McLachlan, A.D., *Acta Cryst. A*, 6 (1982) 871.
- 17 Numerical Algorithms Library Routine (NAGLIB) E04FCC.
- 18 Chau, P.L. and Dean, P.M., *J. Mol. Graphics*, 5 (1987) 97.
- 19 Dean, P.M. and Chau, P.L., *J. Mol. Graphics*, 5 (1987) 152.
- 20 Dean, P.M. and Callow, P., *J. Mol. Graphics*, 5 (1987) 159.
- 21 Dean, P.M., Callow, P. and Chau, P.L., *J. Mol. Graphics*, 6 (1988) 28.
- 22 Goodsell, D.S., *J. Mol. Graphics*, 6 (1988) 41.
- 23 Brickmann, J. and Waldherr-Teschner, M., TH Darmstadt.
- 24 Demole, E., *Helv. Chim. Acta*, 47 (1964) 319.
- 25 Demole, E., *Helv. Chim. Acta*, 52 (1969) 2065.
- 26 Witteveen, J.G. and Van der Weerd, A.J.A., *Rec. Trav. Chim. Pays-Bas*, 106 (1987) 29.
- 27 Brunke, E.J. and Klein, E., *Dtsche. Offenleg.* 2935683 (1979).
- 28 Ohloff, G., Maurer, B., Winter, B. and Giersch, W., *Helv. Chim. Acta*, 66 (1983) 192.
- 29 Nikiforov, A., Jirovetz, J., Buchbauer, G. and Raverdino, V., *Spectros. Int. J.*, 6 (1988) 283.
- 30 Fanta, W.I. and Erman, W.F., *J. Org. Chem.*, 37 (1972) 1624.
- 31 Buchbauer, G., Spreitzer, H. and Zechmeister, F., unpublished results.