

Molecular Similarity Studies on Sandalwood Odour Molecules: Investigations of the Conformational Space^{#,†}

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Summary. Odour differences of some campholene and fencholene derivatives are explained by the analysis of the conformational space and the molecular shape of these molecules. The high flexibility caused by free rotation of some carbon-carbon bonds leads in one case to a large number of energetically possible conformations which have to be taken into account for a study of molecular similarity. In another case, steric restrictions reduce the number of relevant conformations such that no active conformation exists in a thermodynamic equilibrium.

Keywords. Sandalwood fragrance; Molecular similarity; Conformational search.

Molecular Similarity-Studien an Sandelholzriechstoffen. Untersuchungen des Konformationsraumes

Zusammenfassung. Geruchsunterschiede einiger Campholen- und Fencholenderivate werden durch die Analyse der Molekülgestalt und des Konformationsraumes erklärt. Die große Flexibilität dieser Moleküle – bedingt durch die freie Drehbarkeit einzelner Kohlenstoff-Kohlenstoff-Einfachbindungen – führt in einem Fall zu einer großen Zahl energetisch möglicher Konformationen, die bei Untersuchungen der molekularen Ähnlichkeit berücksichtigt werden müssen. In einem zweiten Beispiel reduzieren sterische Wechselwirkungen die Anzahl der Konformationen soweit, daß eine biologisch wirksame Konformation im thermodynamischen Gleichgewicht nicht mehr existiert.

Introduction

Structure-activity relationship is strongly connected with molecular similarity. Molecular surface, molecular shape, conformational space, and electrostatic potentials are features used for the comparison of a set of structurally different molecules with the same biological effect in order to obtain concrete information about structural subunits common for all active molecules. Also, the comparison

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[#] Conformational Calculations on Sandalwood Odour XII; for part XI, see Ref. [1]

with compounds of similar structural or electrostatic properties without the investigated biological effect leads to information about important differences between molecules of various biological properties.

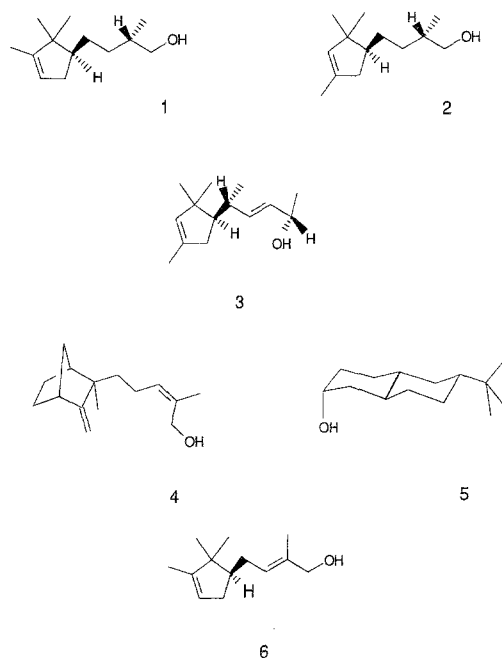
One of the pronounced problems in molecular similarity studies is the large conformational flexibility of molecules with three or more single bonds, a property which very often leads to a great number of local conformational minima. The population of the minima is controlled thermodynamically and can be estimated with the help of the *Boltzmann* statistics. At room temperature, conformations with energies higher than 5 kcal/mol are generally excluded, because their population is too low to contribute to a thermodynamic equilibrium.

In the comparison of *e.g.* molecular surfaces of a set of flexible molecules, the conformational space constructed from all energetically possible conformations, *i.e.* all conformations differing not more than 5 kcal/mol from the lowest-energy conformation, has to be considered. For association processes of a biological active molecule to a convenient receptor site, not necessarily the lowest-energy conformation is responsible. Conformations with higher steric energy may interact more suitably and thus the common structural subunit exists only in these conformations. However, from the energy balance of the association reaction it seems obvious that the activation energy needed to transfer the molecule into a conformation with enhanced energy must not be too high, *i.e.* no rupture of bonds must occur. Molecular similarity investigations on Sandalwood odour molecules have been performed extensively recently [1–3], and a model for osmophoric regions on the molecular surfaces has been developed by Active Analog Approach [4]. In the present paper, some examples of comparison of flexible Sandalwood odour molecules with structurally very similar but odourless molecules are given.

Materials and Methods

The compounds used stem from the group of cyclopentenenes. These substances have become important in the last years. Easy synthetic access and excellent fragrance properties render these products interesting for commercial applications [5, 6]. The main starting component in this group of substances is α -campholene aldehyde ((2',2',3'-trimethylcyclopent-3'-en-1'-yl)-acetaldehyde). *Via* aldol condensation, followed by reduction different alcohols with a woody scent can be synthesized [7]. Among the most important compounds are 4-(2',2',3'-trimethylcyclopent-3'-en-1'-yl)-2-methylbut-2-en-1-ol (Sandacore[®], Sandalmysore[®] Madrol[®], and 4-(2',2',3'-trimethylcyclopent-3'-en-1'-yl)-2-methylbutan-1-ol (Brahmanol[®], (**1**) [8]. The latter is more stable than the unsaturated analogues and therefore preferred for commercial applications. The compounds studied in this investigation are given below.

All shown compounds have one or more chiral centers which give rise to different configurations. Only in few cases some information about the biological effects of the enantiomers is available. In the class of Sandalwood odour compounds it is known that even optical isomers have different fragrance impressions an effect which has been studied extensively for β -santalol (**4**) [10], *tert*-butyl-bicyclodecan-1-ol (**5**) [9, 11] and Madrol (**6**) [12]. It has to be assumed that the association pattern of these isomers at the chiral receptor site is different. Molecule **3** is a fencholene derivative with two methyl groups at position 1 and 4 of the side chain. In an investigation of fencholene derivatives, the fragrance of the isomeric mixture of this compound has been described as woody but not Sandalwood-like [8, 13].



Small structural differences can lead to different biological effects. For instance, Brahmanol[®] (**1**) (campholene skeleton) shows strong sandalwood odour, whereas the analogous compound with a fencholene skeleton (**2**) is odourless [13].

The investigations have been carried out under two aspects: comparison of the conformational space and comparison of the molecular surface using an osmophoric model developed for investigations on compounds with Sandalwood fragrance [3, 4].

The structures of interest were minimized with Allingers MM3 force field program [14]. The different conformations were then obtained by a systematic change of dihedral angles describing the position of the substituents at the free rotatable carbon-carbon single bonds. All these conformations were again minimized and present local minima on the energy hypersurface.

The comparison of the molecular surfaces was performed following procedures reported extensively elsewhere [3, 15, 16]. The applied method is based on the construction of intersection points between the individual *van der Waals* surfaces of the superimposed molecules and a bundle of lines through the geometrical center. The distance between the intersection points of different molecules on one line is a measure for the similarity of the surfaces at the corresponding spatial position.

As a standard for these surface comparisons, the rigid Sandalwood odour molecule *tert.*-butylbicyclodecan-1-ol (**5**) [11] was selected.

Results and Discussion

As a first example for a systematic evaluation of the conformational space, the correlation between the dihedral angles and the energies of the various conformations of compounds **1** and **2** are presented in Fig. 1.

In these diagrams, the energies of the various conformations are plotted in dependence on the relevant dihedral angles. These local minima are connected by solid lines in increasing order of energy. For the dihedral angle α (Fig. 1), the

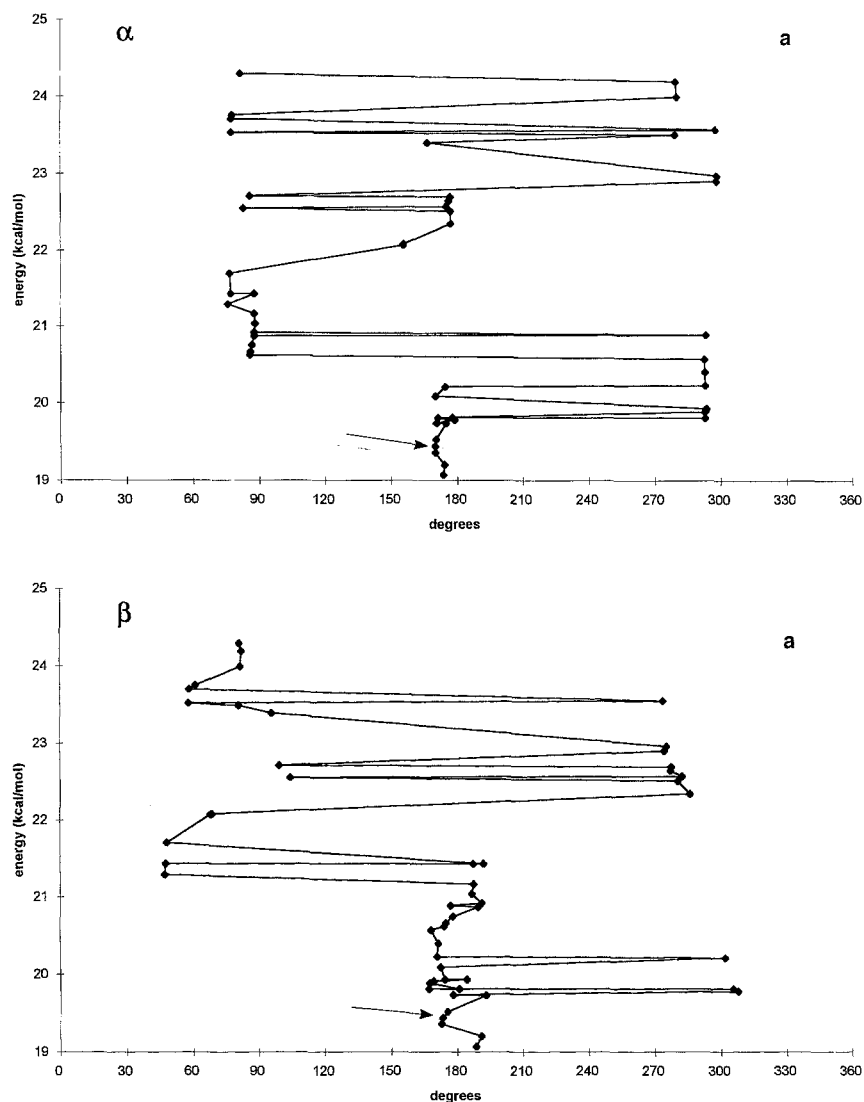


Fig. 1. Energies of the different conformations of **1** (a) and **2** (b) in dependence on the dihedral angles α, β, γ and δ ; the conformations are connected in increasing order of energy; the conformation fitting best to the standard molecule **5** is indicated by an arrow

absolute energy minimum was observed around 170° . The next conformations with slightly increased energy possess the same values for α and β , but different (oscillating) values for the other dihedral angles (not given in the figure). For higher energies, angle ranges between 285° and 310° and between 70° and 95° , were detected for α whereas the corresponding values for β appear between 170° and 205° , between 280° and 310° , and between 40° and 100° , respectively. Conformations with energies higher than 5 kcal/mol above the absolute energy minimum are not shown in the diagrams.

For this first pair of substances, it can be seen that the conformational spaces for every corresponding dihedral angle are very similar. The correlation between the energy of each conformation and the dihedral angle leads to a very similar

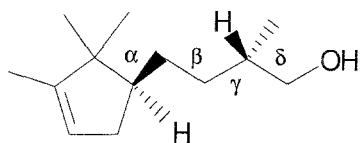
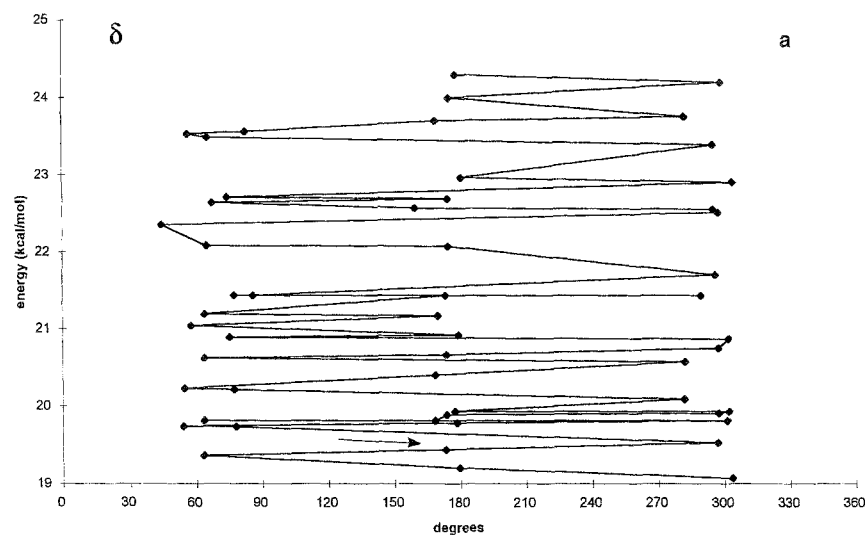
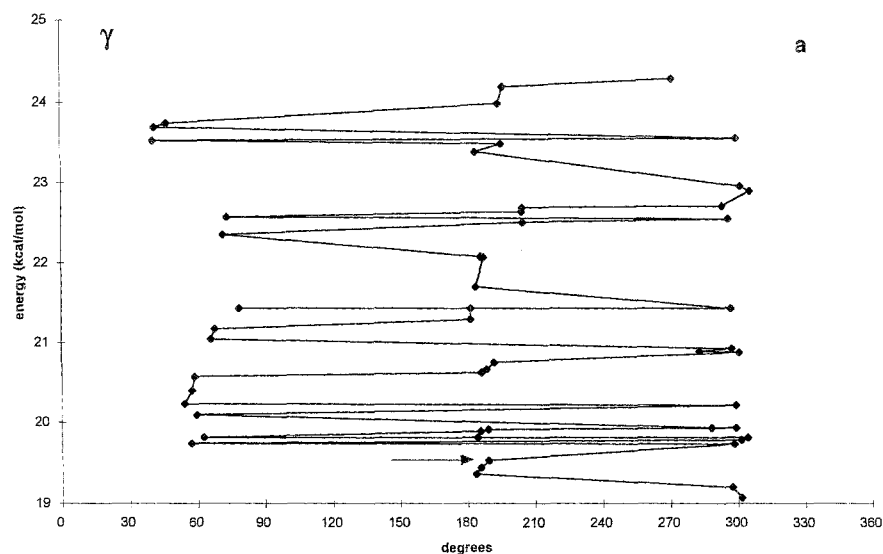


Fig. 1. (Continued)

pattern, although in one region the two compounds differ in the position of a methyl group.

In a molecular surface comparison (using the model of *van der Waals* surfaces) with (+)-*tert.*-butyl-bicyclodecan-1-ol (**5**), a rather rigid compound with strong and clean sandalwood odour used as a standard for the calculations, both substances show similar results in most parts of the molecular surface. All conformations which differ less than 5 kcal/mol from the absolute energy minimum have been

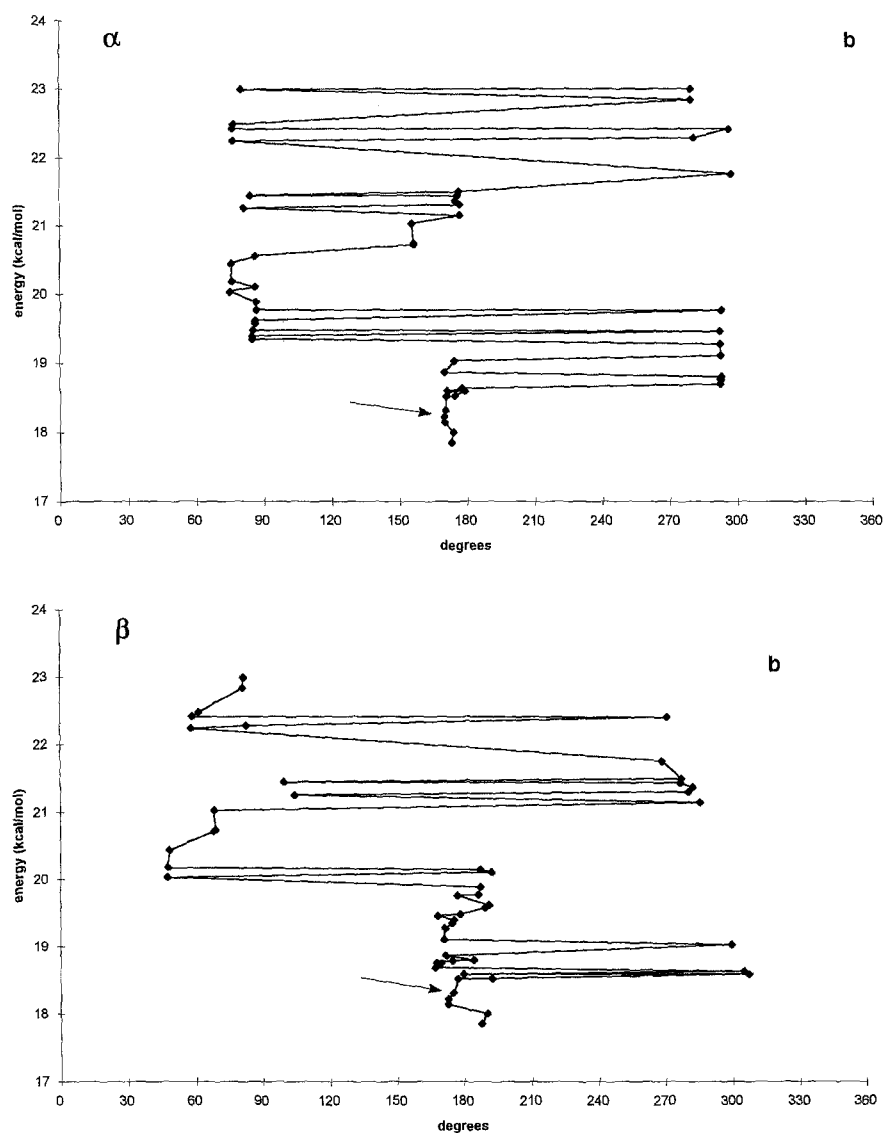


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compared with this reference molecule to find an explanation for the different biological effects in spite of the high structural similarity. The conformations in Fig. 1 indicated with an arrow were found to have the best agreement with the standard compound and were therefore used for a further comparison.

Following the procedure of molecular surface comparison mentioned above, the agreement of the molecular surfaces of the selected conformations of **1** and **2** is close to 100% in large parts of the molecules. In one sector, the agreement is only 47.7%. Using the association model developed by Active Analog Approach investigations [4], osmophoric points were found in both the hydrophilic and the hydrophobic part of the molecule. As the side chains of both molecules are more or less identical and their orientations are not influenced by the substituents at the cyclopentene ring, the osmophoric points found close to the hydroxyl group

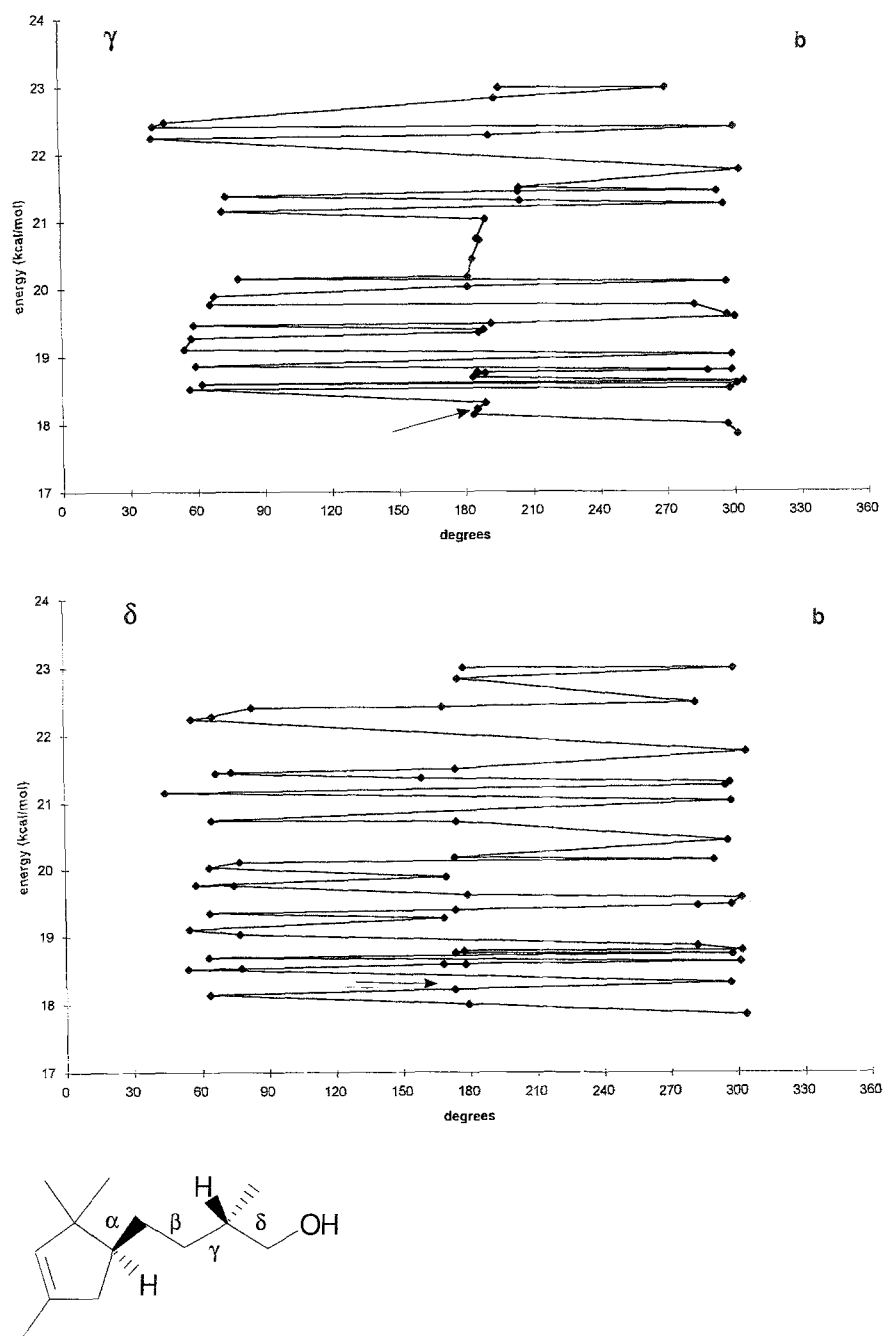


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(hydrophilic molecule part) are also identical. However, the differences at the third osmophoric point, located at the hydrophobic center of the molecule where the methyl group of the fencholene skeleton can be found, lead to an additional surface bulk. This causes a steric repulsion at the receptor site diminishing the association force to such an extent that no Sandalwood fragrance can be detected. In Fig. 2, the bulk at the molecular surface of **2** is shown (dotted black points) in comparison to the molecular surface of Brahmanol[®](**1**) (solid grey surface).

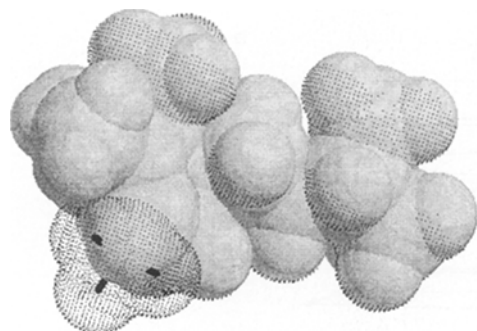


Fig. 2. Superposition of compound **1** (grey solid surface) and **2** (dotted black surface)

As second example of molecules with a flexible side chain, compound **3** was investigated. Fencholenic derivatives have been studied extensively [8, 13] in order to find some Sandalwood odour compounds. In the first example, the substance with the fencholene skeleton (**2**) was found to be odourless because of the deviations of the molecular surface at an osmophoric point. In compound **3**, steric restrictions within the molecule have to be considered.

In most studies, synthetic work starts from the natural optically active fencholene aldehyde which leads to *R* configuration at position 1 at the cyclopentene ring (*1'R*). From the remaining 4 enantiomers, compound **3** (*1'R,5R,2S*) seems to possess the highest similarity to Sandalwood odour molecules. In Fig. 3, the conformational space of compound **3** expressed by the local energy minimum conformations is given.

For compound **3**, one pronounced energy minimum with dihedral angles of $\alpha \approx 290^\circ$, $\beta \approx 130^\circ$, and $\gamma \approx 225^\circ$ can be estimated. Due to steric repulsions within the side chain (interaction between the cyclopentene ring with the methyl group in position 4 as well as interaction between the same methyl group and the allylic

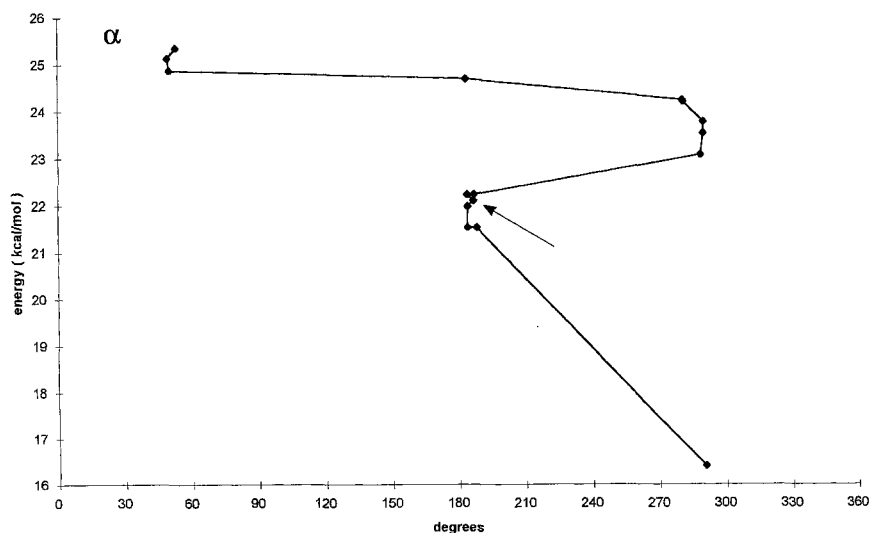


Fig. 3. Energies of the different conformations of **3** in dependence on the dihedral angles α , β and γ ; the conformations are connected in increasing order of energy; the conformation fitting best to the standard molecule **5** is indicated by an arrow

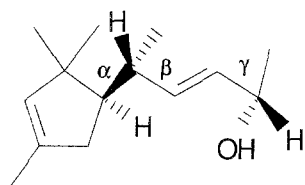
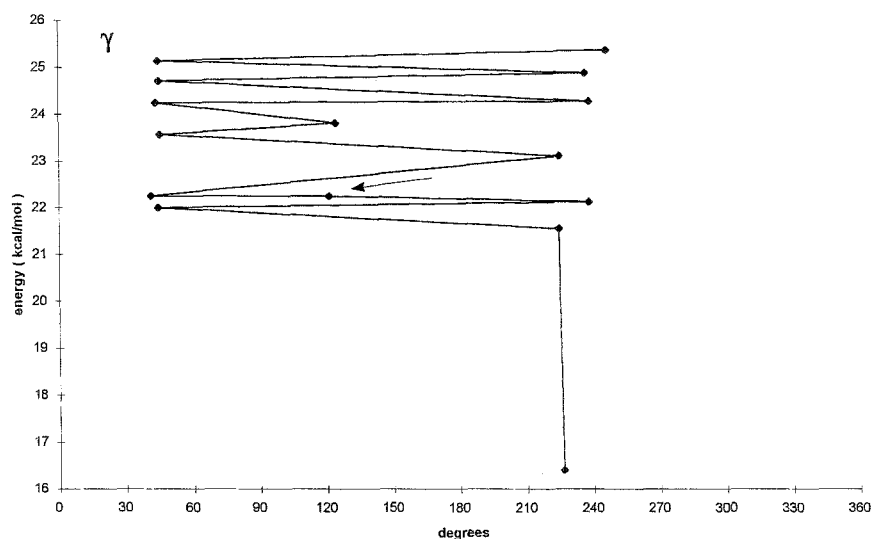
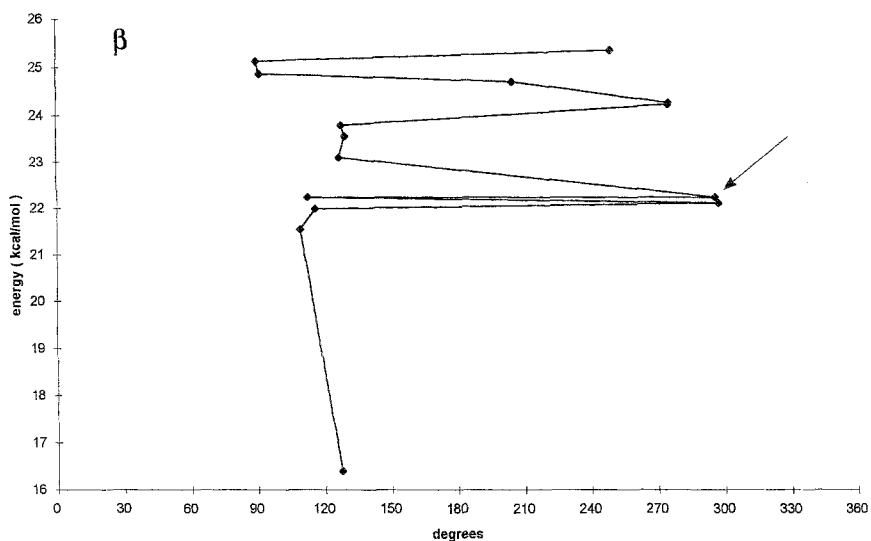


Fig. 3. (Continued)

residue of the side chain), changes of the dihedral angles lead to conformations with significantly enhanced energies. These conformational minima with higher energies possess dihedral angles α around 180° , β around 100° and close to 290° , and γ oscillating between 40° and 245° (Fig. 3). The energies of these conformations are more than 5 kcal/mol (5.15 the lowest but one, 5.59 the next one) higher than the absolute energetical minimum.

Molecular similarity studies on the different conformations show that there is no good agreement between the lowest energy conformation of compound **3** and the Sandalwood standard molecule **5** (common molecular surface less than 32% after surface matching). The conformation which fits best to the standard (common molecular surface 4.45% indicated by an arrow in Fig. 3) and therefore also to the receptor site has an energy of 5.85 kcal/mol above the unfavorable lowest energy conformation. The agreement with the standard molecule **5** being better, Sandalwood odour could be postulated for this conformation. However, the population in a thermodynamic equilibrium in the gas phase is too low to be responsible for the fragrance of the compound which is described to show a weak woody fragrance with a cedric tonality [8, 13].

As a result of the above considerations, it can be stated that it is of importance for the analysis of the molecular shape of Sandalwood odour molecules and related odourless derivatives to consider the agreement of the molecular surfaces with the standard molecule as well as the conformational space which is defined by the structure of all energetically possible conformations, in particular in the case of flexible molecules.

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