Monatshefte für Chemie 119, 711—715 (1988)

Monatshefte für Chemie
Chemical Monthly

Conformational Calculations on Odoriferous Molecules of Sandalwood, I. The Search for the Odoriferous Principle of Sandalwood Oil

Anton Beyer[a], **Peter Wolschann**[a, *], **Armin Becker**[b], **Elisabeth Pranka**[b], and **Gerhard Buchbauer**[b, *]

[a] Institut für Theoretische Chemie und Strahlenchemie, Universität Wien, A-1090 Wien, Austria
[b] Institut für Pharmazeutische Chemie, Universität Wien, A-1090 Wien, Austria

(Received 2 July 1987. Accepted 17 August 1987)

The conformations of two relatively rigid molecules with sandalwood odor have been investigated by molecular mechanics and the semiempirical method AM1. A comparison between both geometries shows that a common structural element exists in the relative rearrangement of a carbinol function and a quarternary carbon atom. The distance of these two centers as well as the electron density agree well in both structures.

(Keywords: Molecular mechanics; AM1; Sandalwood; Conformational calculations)

Rechnungen zur Konformation von Molekülen mit Sandelholzgeruch, 1. Mitt.: Die Suche nach dem Geruchsprinzip des Sandelholzöles

Die Konformationen zweier relativ starrer Moleküle mit Sandelholzgeruch wurden mit molekularmechanischer und mit einer semiempirischen Methode (AM1) bestimmt. Ein Vergleich der beiden molekularer Geometrien zeigt ein gemeinsames Strukturelement und zwar die relative Anordnung der Carbinolfunktion zu einem quartären Kohlenstoffatom. Sowohl deren Abstand als auch deren Elektronendichte stimmen in beiden Verbindungen überein.

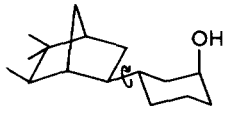
Introduction

The mechanism by which we perceive and discriminate odor is not well understood at present. Not much is known about the nature of the specific receptors and the interaction between the receptors and the odor molecules. Different theories exist to explain the molecular basis of odor perception taking into account mainly the geometry of odor molecules [1–6]. Up to now only a few papers dealing with the structure of the receptor

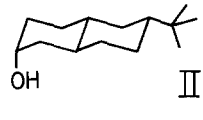
proteins have been published [7–9], from which no general conclusion about the site of the receptor system can be drawn. Commonly it is accepted that the geometry of odor molecules is one of the most important factors for the specific interaction with the receptor leading to the nerve impulse. A survey of the present state of the molecular basis of olfaction has been given recently [10].

An interesting system for the study of a series of odoriferous compounds are the molecules of sandalwood fragrance. More than 70 different odor molecules are known of that typical woody character, molecules of different geometry and with different functional groups [11, 16]. If there is an odoriferous principle in the geometries of this relative large number of different molecules it might be found by comparison of their geometries and their possible conformations.

In the present paper we present a conformational analysis of two more or less rigid odor molecules of sandalwood character. The molecular conformations were estimated by molecular mechanics, in particular with the program package MOLMEC [12]. The electronic properties of these compounds were calculated using the semiempirical program AM1 [13, 14].



I



II

Results and Discussion

Camphenylcyclohexanol (I) consists of a rigid bicyclic system connected to a cyclohexanol ring. It has been shown that the equatorial-axial positions of both substituents at the cyclohexane ring is essential for its odor properties, in addition, the position of the hydroxyl group must be in 3-position to the bicyclus [17]. The carbon-carbon bond between both ring systems allows restricted rotation giving three energy minima. Inversion of the cyclohexane ring creates a conformation, where the hydroxyl group is in equatorial position and the bicyclus is bound axially to the cyclohexane ring. The four conformers of lowest energy of (I) are given in Table 1. The other possible conformations are of much higher energy (> 14.6 kJ/mol) due to steric interactions and they would not be populated at thermodynamic equilibrium at room temperature. The dihedral angle α between norbornane and cyclohexane ring is included in Table 1. The conformers of (I) are plotted in Fig. 1. The skeleton of the cyclohexane ring is kept constant in all conformations whereas the degree of freedom of the rotation of the carbon-carbon single bond together with

Table 1. *Lowest energy conformations of (I) calculated by MOLMEC* (Energies in kJ/mol, angles in degrees)

Energy	Dihedral angle
168.9	179.2
174.3	291.6
173.4	56.6
171.8	178.0

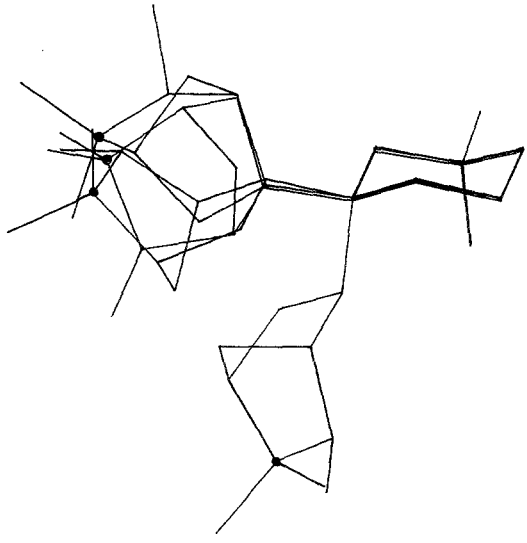


Fig. 1. Low energy conformations of (II)

the ring inversion is demonstrated in the figure. The position of the quarternary carbon atom as a center of high electron density is marked.

The decalinol (II), a new synthetic sandalwood odor compound with pronounced fragrance [15], is an extremely rigid molecule, suitable for a structural comparison. Its conformation was also calculated by MOLMEC, the rotation of the *t*-butyl group leads to three identical structures. For comparison of (I) and (II) the electron densities were calculated by the semiempirical program AM1. In Fig. 2 the electron densities are given for the determined force field geometries of (II) and that conformation of (I) which fits best to the structure of (II). As indicated in Fig. 2 there is a good agreement of the electron densities at the five carbon atoms connecting the hydroxyl group and the quarternary carbon. Such a

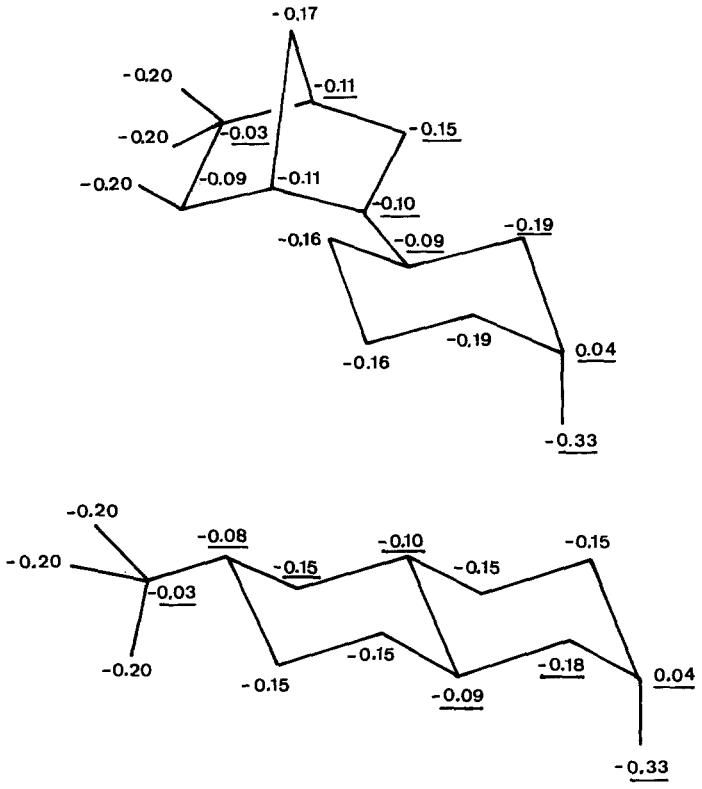


Fig. 2. Net charges of the best fitting conformation of (I) and of (II)

distance between the hydroxyl group and a bulky group has been proposed earlier to be essential for the odor activity of sandalwood molecules [15]. From the electronic point of view this structural element exists in both compounds in a similar geometry as the distance between the hydroxyl group and the quarternary carbon atom was estimated as 7.1 Å for (II) and 7.2 Å for the best fitting conformation of (I). An axial hydroxyl group as the center of highest electron density is present in both structures, it is therefore in an outstanding position, which might be of importance for the activity of these compounds.

For a more detailed analysis of the common structural elements the findings of this investigation will be supplied by comparison of the molecular shape of other odor molecules of sandalwood character.

Acknowledgement

The authors want to thank Prof. *P. Schuster* for helpful discussions.

References

[1] *Amoore JE* (1970) Molecular basis of odor. Charles Thomas, Springfield, p 773
[2] *Boelens H, Haring HG, Takken HJ* (1983) Chem Ind 3: 27
[3] *Ohloff G, Giersch W, Thommen W, Wilhalm B* (1983) Helv Chim Acta 66: 1343
[4] *Buchbauer G, Wiltschko M* (1978) J Soc Cosmet Chem 29: 307
[5] *Jurs PC, Ham CL, Brügger WE* (1981) ACS-Symposium Series 148: 143
[6] *Beets MGJ* (1982) In: *Theimer ET* (ed) Fragrance chemistry. The science of the sense of smell. Academic Press, New York, p 77
[7] *Pevsner J, Trifiletti RR, Strittmatter StM, Snyder SH* (1985) Proc Natl Acad Sci USA 82: 3050
[8] *Bignetti E, Tirindelly R, Rossi GL, Bolognesi M, Coda A, Gatti G* (1985) J Mol Biol 186: 211
[9] *Heck G, DeSimone JA, Persaud K* (1986) Biophys J 49: 182a
[10] *Ohloff G* (1986) Experimentia 42: 271
[11] *Brunke E-J, Klein E* (1982) In: *Theimer ET* (ed) Fragrance chemistry. The science of the sense of smell. Academic Press, New York, p 397, and references cited therein
[12] *Beyer A*, in preparation
[13] *Dewar MJS, Zoebisch EG, Healy EF, Stewart JP* (1985) J Am Chem Soc 107: 3901
[14] *Dewar MJS, Dieter KM* (1986) J Am Chem Soc 108: 8075
[15] *Witteveen JG, Van der Weerdt AJA* (1987) Recl Trav Chim Pays-Bas 106: 29
[16] *Jelinek E* (1985) Work for diploma; University of Vienna
[17] *Demole E* (1964) Helv Chim Acta 44: 1766