158. Investigation of an Olfactoryly Active Ring-Like Conformer of a Chain-Type Odorant, (3*S*)-3,7-Dimethyloctanal, by Computer Calculation and Graphics

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The odor of (3*S*)-3,7-dimethyloctanal, a chain-type odorant, has some resemblance to that of ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate, a ring-type odorant. We investigated the ring-like conformers of (3*S*)-3,7-dimethyloctanal. Two approaches, *i*) systematic conformational analysis and *ii*) construction of the initial structure by referring to the structure of the ring-type odorant, were considered in the search for ring-like conformers of the chain-type odorant. As a result, it was found that two stable ring-like conformers of (3*S*)-3,7-dimethyloctanal, obtained from the two approaches, resembled conformers of ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate in their three-dimensional structural features. The shapes of the two ring-like ones were not exactly the same but were quite similar. Therefore, the two ring-like conformers were considered to approximate the olfactoryly active conformer that binds and stimulates the same odor receptor as that for ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate. In addition, ring-like conformers of another chain-type odorant, 2-methylpent-2-enal, were investigated to check the validity of the calculation method used.

1. Introduction. – Odoriferous compounds are classified as ring-type and chain-type molecules from the point of structure. A quantitative or qualitative structure-activity relationship (QSAR) study of some ring-type odorants was performed with consideration of their conformations [1] [2]. On the other hand, possible olfactoryly active conformers of chain-type odorants were not significantly discussed, in spite of the report that both

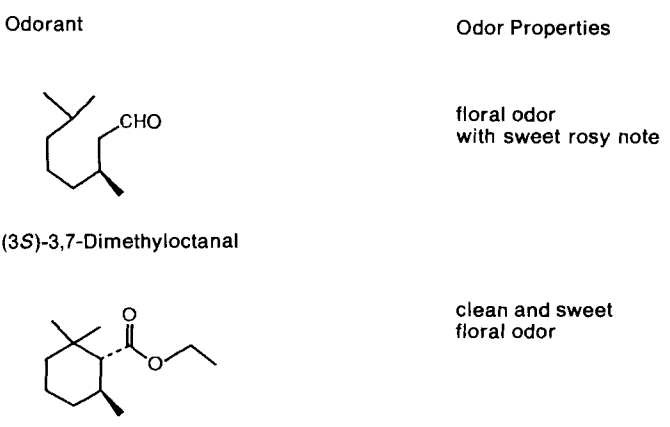
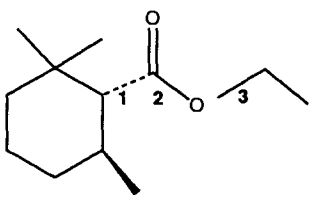


Fig. 1. *Odor properties of (3S)-3,7-dimethyloctanal and ethyl (1R,6S)-2,2,6-trimethylcyclohexane-1-carboxylate*

chain-type and ring-type molecules exist for many odor qualities as minty, camphory, woody, amber, musk, and civet [3]. It is assumed that three-dimensional (3-D) structures of chain-type odorants are similar to those of ring-type odorants at the odor receptor as long as their odor qualities are similar. However, the following questions have not been answered: *1*) is it possible for a ring-like conformer of a chain-type odorant to exist based on stability? and *2*) how much of the ring-like conformer of a chain-type odorant is similar to a ring-type odorant?

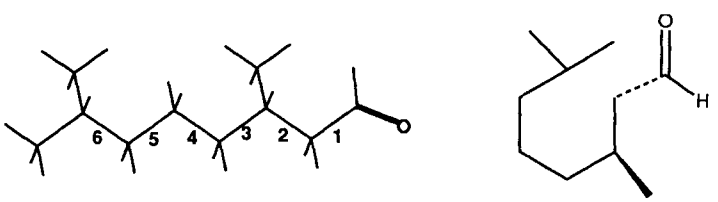
In this study, (3*S*)-3,7-dimethyloctanal, considered a chain-type odorant, and ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate, considered a ring-type odorant, were selected, since evaluation of their odor properties were reported as shown *Fig. 1* [4]. We considered that the two molecules had some odor similarity.

2. Methods. – 2.1. *Construction of the Starting Structures and Conformers.* Starting structures (*Fig. 2*) were constructed by *ChemDraw 2.13* and *Chem3D 2.0* [5] on an *Apple Macintosh IIcx* computer. One initial structure (RING) was constructed for ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate. Two different initial structures (CHAIN-C and CHAIN-R) were constructed for (3*S*)-3,7-dimethyloctanal.



Ethyl (1*R*,6*S*)-2,2,6-Trimethylcyclohexane-1-carboxylate

(RING)



(3*S*)-3,7-Dimethyloctanal

(CHAIN-C) (CHAIN-R)

Fig. 2. *Initial structures and selected bonds rotated for conformational analysis*

Conformers of RING, CHAIN-C, and CHAIN-R were generated as follows. For RING, 432 ($2 \times 6 \times 6 \times 6 = 432$) conformers were obtained, since two conformers of the tetra-substituted cyclohexane ring were considered and each dihedral angle of three bonds shown in *Fig. 2* was changed to 0°, 60°, 120°, 180° −120°, and −60° (six different angles). For CHAIN-C, 729 ($3 \times 3 \times 3 \times 3 \times 3 \times 3 = 729$) conformers were obtained, since each dihedral angle of six bonds in *Fig. 2* was changed to 60°, 180°, and −60° (three

different angles). CHAIN-R was constructed afterwards by modifying the optimized structures of RING after conformational analysis and structure optimization.

2.2. *Conformational Analysis, Strucutre Optimization, and Selection of Conformers.* For RING and for CHAIN-C, conformational analysis was done by calculating the total energy value [eV] of the fixed structure of each conformer. Structure optimizations of the conformers based on bond lenghts, bond angles, and dihedral angles were carried out in succession. Software and hardware used for the calculations were PM3 (MOPAC Ver. 5.01) [6] and *Sony* computer *NWS-830*, respectively. A small number of conformers for comparison were selected by the following *Procedure*: *a*) after conformational analysis, the conformer with the lowest energy and those with a little higher energy (within 10.0 kcal/mol ≈ 41.8 kJ/mol) were picked up, *b*) structural features of the conformers were taken into consideration and further deletion of the conformers was done, and *c*) after structure optimization of the selected conformers, the conformer with the lowest energy and those with slightly higher energy (within 2 kcal/mol ≈ 8.4 kJ/mol) were used.

The initial structures of CHAIN-R, constructed by referring to the RING conformers selected by the procedure *a* and *b*, were optimized by PM3 and selected by the procedure *c*.

2.3. *Comparison of 3-D Structures.* Graphic images of a small number of selected conformers were compared and their structural differences were calculated as root mean square (RMS) error values [Å] using least-squares-fit method of MidasPlus on a *IRIS 4D/420GTX* computer. The MidasPlus software system is from the Computer Graphics Laboratory, University of California, San Francisco, USA [7].

2.4. *Validation of the Calculation and Searching Method for Ring-Like Conformer of Chain-Type Odorant.* To confirm the validity of the method used in this work, other odorants that possess bitter almond odor were chosen and calculated; 2-methylpent-2-enal as a chain-type and benzaldehyde as a ring-type odorant were chosen from the report of *Boelens* and *Heydel* [8]. The methods used were the same as *2.1–2.3* explained above.

3. Results. – 3.1. *Selection of Conformers.* The number of conformers selected is shown in *Table 1*. For selection of RING conformers by structural features (*Procedure b*), the difference in dihedral angles of bond 1 of RING in *Fig. 2* was taken into consideration. For selection of CHAIN-C conformers by structural features (*Procedure b*), the longest side length of the circumscribed box (LLCB) was used as a parameter for the size of molecule. The LLCB parameter was explained as 'the longest side length of the circumscribed hexahedron' in our preceding work [1]. *Fig. 3* shows 170 conformers of

Table 1. *Number of Selected Conformers*

Name	No. of conformers initially constructed	No. of conformers selected after conformational analysis (*a*)	No. of conformers selected by structural features (*b*)	No. of conformers selected after optimization (*c*)
RING	432 conformers	73 conformers	11 conformers	3 conformers
CHAIN-C	729 conformers	170 conformers	3 conformers	3 conformers
CHAIN-R				2 conformers

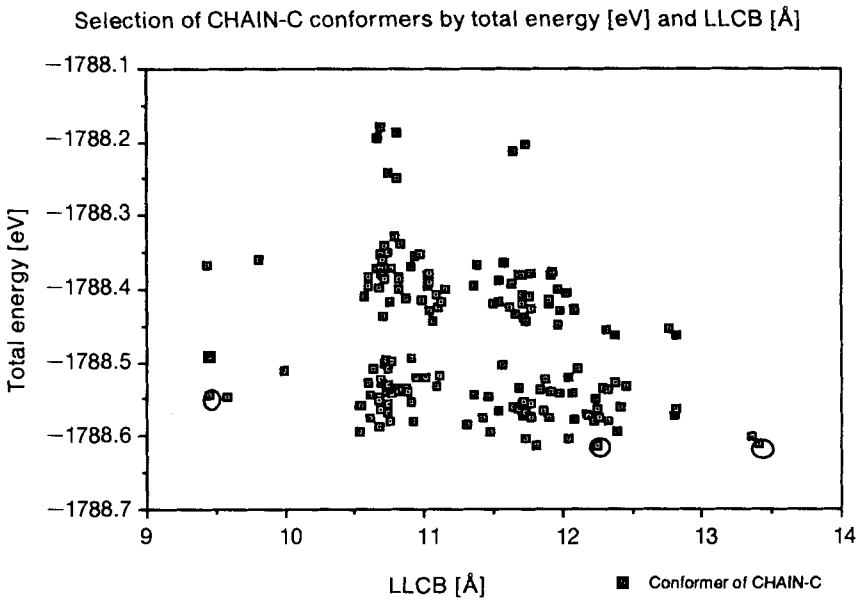


Fig. 3. *Selection of CHAIN-C conformers by total energy* [eV] *and LLCB* [Å]

CHAIN-C plotted by total energy [eV] *vs.* LLCB [Å]. The selected three conformers are circled in *Fig. 3*; one had the lowest total energy, another had low total energy and short LLCB, and the other had the longest LLCB. The last one was a stretched long-chain conformer and selected for comparison. Further selection of conformers of RING and CHAIN-C were done using procedure *c*. Four initial structures of CHAIN-R were constructed from the optimized structures of the RING conformers and two conformers were selected using *Procedure c*.

3.2. *Total-Energy Values of Selected Conformers. Table 2* shows the names of selected conformers for convenience, actual total-energy values [eV], and difference in total-

Table 2. *Total-Energy Values and Difference of Energy Values* (ΔE)

Name of selected conformers	Total-energy values [eV]	ΔE [kcal/mol]
RING # 1[a])	−2350.38926	0.00
RING # 2	−2350.3272	1.43
RING # 3	−2350.31957	1.61
CHAIN-C # 1	−1788.75456	0.28
CHAIN-C # 2	−1788.75288	0.32
CHAIN-C # 3	−1788.74485	0.50
CHAIN-R # 1[b])	−1788.76668	0.00
CHAIN-R # 2	−1788.70048	1.53

[a]) The lowest-energy conformer of ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate.

[b]) The lowest-energy conformer of (3*S*)-3,7-dimethyloctanal.

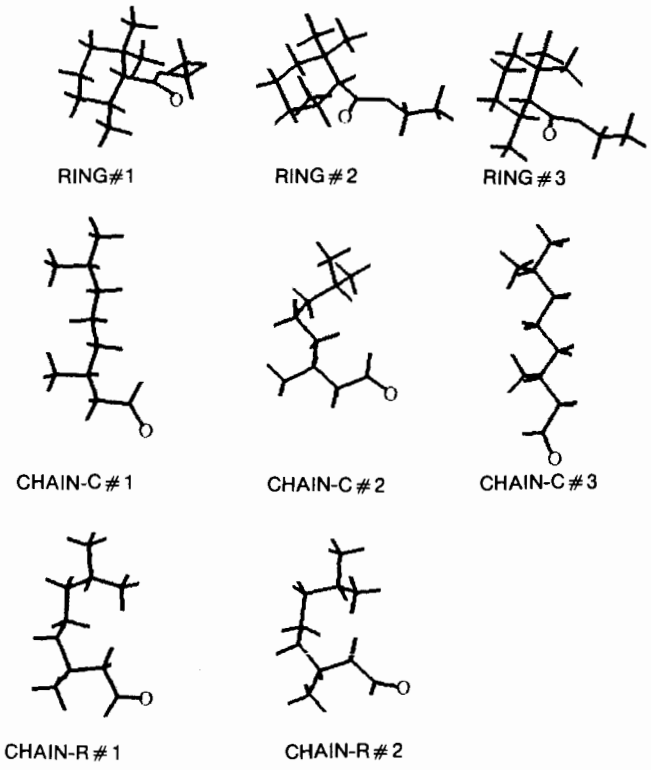


Fig. 4. *Selected conformers of ethyl (1*R,6S*)-2,2,6-trimethylcyclohexane-1-carboxylate and (3*S*)-3,7-dimethyl-octanal* (O indicates an O-atom of a C=O group)

energy values [kcal/mol] compared with the lowest energy conformer of each odorant. The skeletons of eight selected conformers are shown in *Fig. 4*.

3.3. *Difference in 3-D Structural Features of Selected Conformers. Table 3* and *4* show the RMS error values calculated by the 11 points matching of two conformers and seven points matching of two conformers. The 11 atoms were heavy atoms common in (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate and (3*S*)-3,7-dimethyloctanal. The seven atoms in *Fig. 5* were used for superimposing, since the dimethyl groups and one methyl

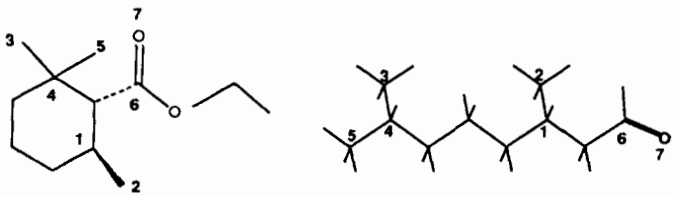


Fig. 5. *Seven selected atoms for matching*

Table 3. *RMS Error Values* [Å] *of Two Conformers by 11-Points Matching*

Name of conformers	RING # 1	RING # 2	RING # 3
CHAIN-C # 1	2.39	2.13	2.39
CHAIN-C # 2	1.44	1.63	1.42
CHAIN-C # 3	2.6	2.48	2.59
CHAIN-R # 1	1.42	1.36	1.55
CHAIN-R # 2	1.06	1.47	1.06

Table 4. *RMS Error Values* [Å] *of two Conformers by 7-Points Matching*

Name of conformers	RING # 1	RING # 2	RING # 3
CHAIN-C # 1	2.39	2.05	2.4
CHAIN-C # 2	1.21	1.3	1.28
CHAIN-C # 3	2.68	2.8	2.6
CHAIN-R # 1	1.56	1.43	1.65
CHAIN-R # 2	1.20	1.51	1.17

group were considered to relate to the molecular shape including thickness or bulkiness, and a carbonyl group was a common functional group. Large RMS error values mean that the 3-D structures of the two conformers are different. From *Table 3*, CHAIN-R # 2 was considered similar to RING # 1 and RING # 3. However, when focused on seven atoms in the conformers (*Table 4*), both CHAIN-C # 2 and CHAIN-R # 2 were similar to RING # 1 and RING # 3. Graphic images of CHAIN-C # 2, and CHAIN-R # 2 with RING # 1 by seven points matching are shown in *Fig. 6*. Rather bulky or thick structures consisting of hydrocarbons were seen in common, and each of the O-atoms occupied similar spacial positions in CHAIN-C # 2, CHAIN-R # 2, and RING # 1. The RMS error value between CHAIN-C # 2 and CHAIN-R # 2 was 0.51 Å. Shapes of CHAIN-C # 2 and CHAIN-R # 2 by seven points matching were quite similar as shown in *Fig. 6*. On the other hand, CHAIN-C # 3, a stretched long-chain conformer, was considered different from RING # 1, RING # 2, and RING # 3. In *Fig. 6*, RING # 1 was shown, since RING # 1 and RING # 3 were considered similar when focused on the seven atoms. The RMS error value between RING # 1 and RING # 3 was 0.51 Å.

3.4. *Application of the Calculation Method to Bitter Almond Odorants.* The conformers selected were shown in *Fig. 7*. ring # 1 was the only conformer of benzaldehyde. chain-c # 1 was the most stable conformer and chain-c # 4 was the conformer of the longest LLCB obtained by conformational analysis. chain-c # 2, chain-c # 3 and chain-c # 5 were stable and compact conformers; in this case, three stable and compact conformers were selected, since the differences of total energy and LLCB of the three conformers were very small. chain-c # 4 was shown for a comparison. chain-r # 1 and chain-r # 2 were constructed by referring to benzaldehyde and structurally optimized. Energy differences of chain-c # 1, chain-c # 2, chain-c # 3, chain-c # 4, chain-c # 5, chain-r # 1 and chain-r # 2 were within 1.5 kcal/mol ($\approx$ 6.3 kJ/mol). The corresponding RMS error values of

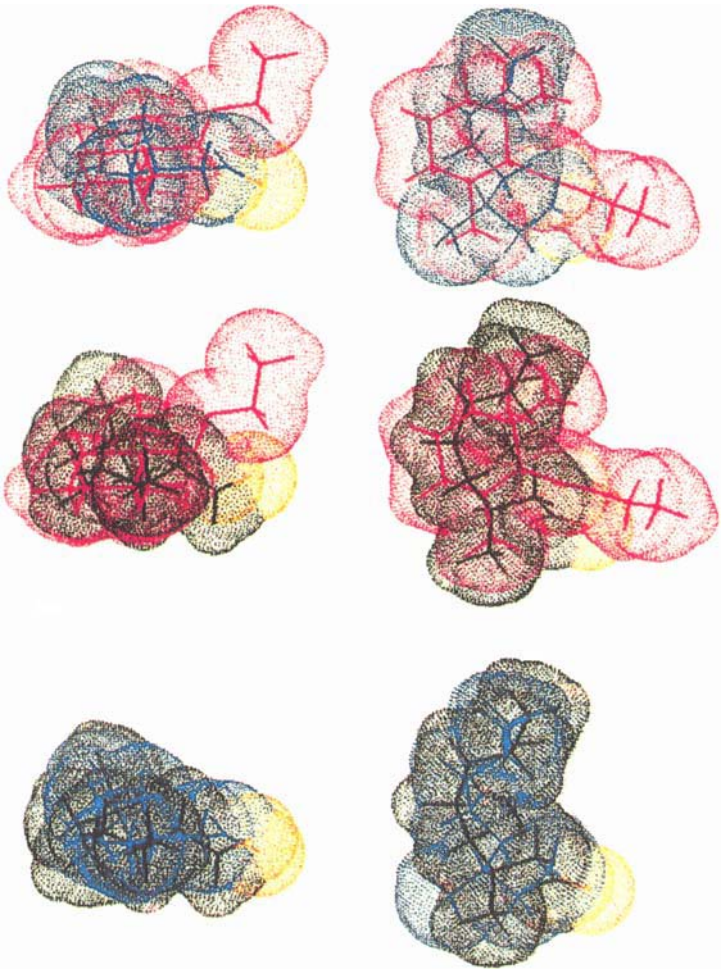


Fig. 6. *Graphic images of CHAIN-C # 2* (blue), *CHAIN-R # 2* (black), *and RING # 1* (magenta) *from two different directions* (O-atom in C=O group was shown by orange color). *Top:* CHAIN-C # 2 with RING # 1; *middle:* CHAIN-R # 2 with RING # 1; *bottom:* CHAIN-C # 2 with CHAIN-R # 2.

chain-c # 2, chain-c # 3, chain-r # 1, and chain-r # 2 with ring # 1 were between 0.44 to 0.46 Å by seven points (heavy atoms) matching. Among the four conformers (chain-c # 2, chain-c # 3, chain-r # 1, chain-r # 2), chain-c # 2 and chain-r # 1 were considered quite similar; the RMS error value of the two by the seven points matching was 0.01 Å.

4. Discussion. – 4.1. *Possible Olfactoryly Active Conformer.* It was best to select one reliable conformer of ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate for comparison, if possible. But all three conformers were used, since no representative structure model for floral odor has been established. From the comparison of conformer's total

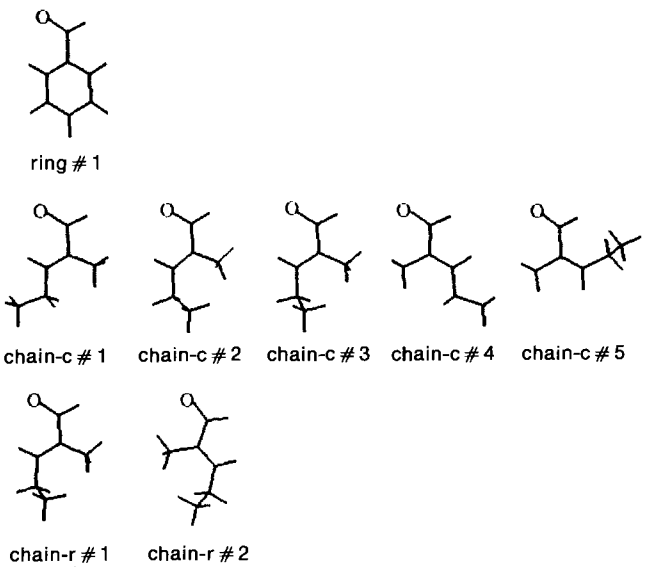


Fig. 7. *Selected conformers of benzaldehyde and 2-methylpent-2-enal* (O indicates an O-atom)

energies, four conformers of (3*S*)-3,7-dimethyloctanal in *Table 2* were considered to be as stable as a stretched conformer. The graphic images of the two ring-like conformers (CHAIN-C # 2 and CHAIN-R # 2) resembled the image of RING # 1 and RING # 3. The 3-D structures of the two ring- like conformers were similar each other, though they were obtained from two different approaches.

In addition, the calculation method was applied to another odorant, 2-methylpent-2-enal, and the obtained results were reasonable and not contradictory to those of (3*S*)-3,7-dimethyloctanal. The conformers selected for 2-methylpent-2-enal were also stable and structurally resembled to benzaldehyde, ring-type odorant (ring # 1). The two ring-like conformers (chain-c # 2 and chain-r # 1) were quite similar, though they were obtained from two different approaches.

Therefore, in both cases it is considered that the two ring-like conformers, CHAIN-C # 2 and CHAIN-R # 2 (or chain-c # 2 and chain-r # 1), approximate the olfactoryly active conformer that binds and stimulates the same odor receptor as that for ring-type odorant, ethyl (1*R*,6*S*)-2,2,6-trimethylcyclohexane-1-carboxylate (or benzaldehyde). The active conformer, approximated by CHAIN-C # 2 and CHAIN-R # 2 (or chain-c # 2 and chain-r # 1), is considered to be formed by interaction with odor receptor and to bind the odor receptor. Experimental evidence concerning odorant-receptor interaction has not yet been established by X-ray or NMR studies, though it is desired strongly.

4.2. *Ring-Like Conformers of Odorants.* The search for ring-like conformers of chain-type odorants was considered useful for a better QSAR study of odorants for two reasons: *a*) the existence of odorant specific receptor protein that requires 3-D structural complementarity of odorants to receptor was supported by the finding of *Buck* and *Axel* [9]; and *b*) it was pointed out that odor ligands and neurotransmitter ligands have

similarities in size and in the presence of a partial or complete ring structure [10]. In addition, the search for ring-like conformers of odorants is useful to discuss the interaction of a chain-type odorant with odorant-specific receptor protein, when the receptor protein is identified in the near future, since an odorant specific receptor protein is predicted as a 7-TD protein like the β-adrenergic receptor.

4.3. *Calculation Method.* Two approaches, *i*) systematic conformational analysis and *ii*) construction of initial structures by referring to structures of ring-type odorants, were used in the search for ring-like conformers of chain-type odorants by calculation. The result gave quite similar conformers which were considered to approximate the active conformers. The use of the two approaches jointly was considered effective, since it succeeded in both cases of (3*S*)-3,7-dimethyloctanal and 2-methylpent-2-enal. Approach *i* may be useful to predict active conformers of the ring-type odorants, since it is quite difficult to determine the possible conformation of the ring-type odorants like macro cyclic musks without X-ray analysis. Approach *ii* saves computation time to search for ring-like conformers of chain-type odorants.

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