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Point-fluorination effect on molecular conformation in the aggregation pheromone, (*3S,4S*)-4-methyl-3-heptanol.

Shuichi HAYASE*, Ayako TANAKA, Motoi KAWATSURA,
and Toshiyuki ITOH*

Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, 4-101 Koyama-Minami Tottori, 680-8552, JAPAN
shu@chem.tottori-u.ac.jp

1. Introduction

Attention is growing about the subject of chemical communication among insects. The most striking example of specificity is the ability of the olfactory receptors to discriminate between enantiomers and many interesting results have been reported on the relationship between activities and stereochemistry of pheromone molecules. Mori established that there are at least ten categories of stereochemistry-pheromone activity relationships [1]. However, the molecular basis of their outstanding specificity is far from being totally understood. We have been investigating the fluorine substitution effect on the EAG activities of the insect pheromone, Eldanolide, and established that differences in the populations of favorable conformers of the fluorinated analogues of this pheromone best explain the differences in biological activity according to the position of fluorination [2,3]. Pingnatello and co-workers reported that a significant reduction of the pheromone activity was obtained when 2-position of (3*S*,4*S*)-4-methyl-3-heptanol (**1**), which is known as the aggregation pheromone of the elm bark beetle, was modified by difluorination: (3*R*,4*S*)-2,2-difluoro-4-methylheptan-3-ol (**2**) showed a slight pheromone activity [4]. There has been no discussion reported, however, on the origin of the reduced activity caused by the fluorine-substitution from the standpoint of conformer pattern of these compounds. We expected that conformational analysis of **1** and its difluorinated analogues might provide useful information for considering the molecular based knowledge of chemical communication among insects and might make it possible to design artificial pheromone compounds superior to the natural one. Here we wish to report the results of conformation analysis of (3*S*,4*S*)-4-methyl-3-heptanol (**1**) and two types of difluorinated analogues **2** and **3** (Figure 1).

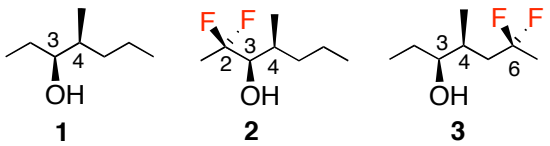

Fig.1. (*3S,4S*)-4-methyl-3-heptanol (**1**) and its fluorinated analogues **2** and **3**.

2. Method

We performed B3LYP level analysis of compounds **1-3** and attempted to find the relationship between the activity and their conformation. In particular, occurrence probability for the stable conformations of the three molecules **1**, **2** and **3** was investigated. The calculation started at energy scans for the C-C bonds in the compounds **1-3**. AM1 optimization was performed by fixing the dihedral angles of D_1=$C^1C^2C^3C^4$, D_2=$C^2C^3C^4C^5$, D_3=$C^3C^4C^5C^6$, D_4=$C^4C^5C^6C^7$, and D_5=$C^4C^3O^9H^{10}$

on G+(60°), T(180°), or G-(-60°). Although 81 (D_1, D_2, D_3, D_4)-conformations were possible for one D_5 conformation, we selected 16 types of conformers from among for the D_5 conformations and conducted detailed calculations. The full optimization of each conformer in **1-3** has been performed by B3LYP/6-31++G** followed by vibrational analysis.

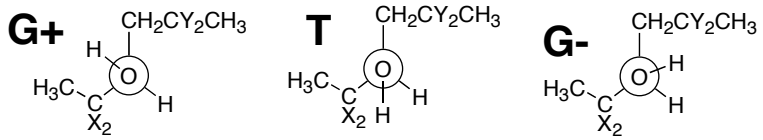

Fig.2. Stable D_5 conformations around the C^3-O bond in **1-3**.

The population of these three stable D_5 conformers (see Fig. 2) was estimated by the sum of the probability of occurrence of the 16 main-chain conformers with the same D_5 conformation.

3. Results and Discussion

Three stable D_5 conformations (G-, T, G+) were attained for compounds **1-3** as shown in Figure 2 and the results of population pattern analysis of these compounds are described in Figure 3. The population pattern of compound **2** was completely different from that of natural pheromone **1**. Especially, a significant reduction of population of the G- conformer was observed compared to that of **1**. On the other hand, the population pattern of **3** is similar to that of natural pheromone **1**, while a certain difference in population ratio was obtained between **1** and **3**. We assume that these differences in population pattern might be derived from the O-H-F hydrogen bond found in compound **3**.

We hypothesize that G- conformer may be the most important active conformer having high affinity towards pheromone receptor proteins because compound **2** showed loss of the pheromone activity [4]. Since a slight reduction of G- conformer ratio is observed for compound **3** compared to **1**, we are now anticipating that the pheromone activity of **3** may be lower compared to the natural pheromone, but that **3** might show a certain pheromone activity. To confirm this prediction, synthesis of enantiomerically pure **3** is now ongoing.

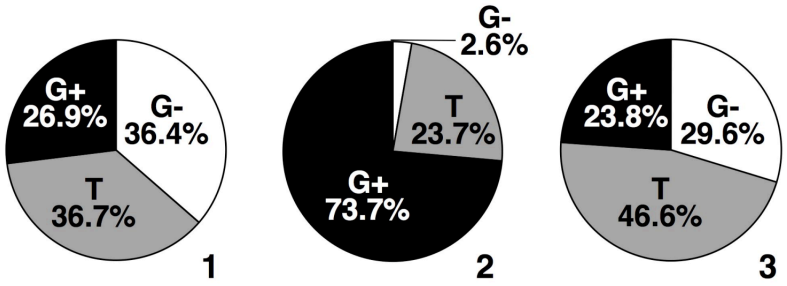

Fig.3. Probability of occurrence of the D_5 conformers in vacuo for compounds **1-3**.

References

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