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Molecular Origin of the Recognition of Chiral Odorant by Chiral Lipid: Interaction of Dipalmitoyl Phosphatidyl Choline and Carvone

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We present the first effective pair potential (EPP) based theory of recognition of chiral odorant molecule (carvone) by a chiral lipid (dipalmitoyl phosphatidylcholine). The theory explains the experimentally observed preference of the interaction of the lipid with one particular enantiomer of carvone over the other. The theory also reveals interesting discrimination effects, which have significance in the chiral recognition process.

1. Introduction

The interaction of an odorant molecule with the lipid molecule of the mucous layer in the olfactory region as well as those present in the cell membrane in the olfactory neuron is a primary and important step in the odor reception. The lipid molecules in the mucous layer help in transporting the soluble odorant molecules to interact with the olfactory receptors, and the interaction leads to sensory transduction. The human olfactory system can discriminate between subtle differences in the chirality of the two enantiomers. The (*S*)-(+)-carvone has a caraway-like smell, whereas the (*R*)-(−)-carvone has a spearmint-like smell and the later is a stronger odorant on the threshold basis.[1] Several other examples of different odors of enantiomeric molecules are known.[2] With the transmembrane receptor helices[3] being chiral, it is expected that the interaction between receptor and chiral odorant will be dependent on their specific enantiomeric structure. A molecular understanding of the interaction in biological or biomimetic molecules, which depends on the chiral structure of related molecules, is of tremendous importance. Nature has strong chiral preference, which is related to the yet unresolved problem of understanding the *origin of homochiral evolution* on earth.[4] Natural biomolecules such as proteins lose their functionality if the chirality of their basic units (amino acids) is changed. Similarly, the natural DNA is made only by enantiomerically pure sugar and the membrane is made by enantiomerically pure lipid. It is now well-known that there is a direct correlation between the chirality at various levels of structural hierarchy at least in biomimetic systems.[5] Thus, it is important to understand the role of chirality in odor recognition process. It is important to note that the preferential interaction of enantiomeric lipid with one particular enantiomer of the odorant will lead to a more effective interaction with the receptor compared to the other enantiomer. As a result, the molecular recognition of the chiral odorant by the membrane lipid is important but yet to be understood in detail.[6] It is pointed out recently[7] that the importance of the chirality of the lipid (and odorant) in odor perception does not contradict the known role of the receptor proteins but reveals another facet of the problem of understanding the odor recognition process. The monolayers of *R* (−) and *S* (+) carvone and the L-DPPC molecule are experimentally studied as an *in vitro* model of chiral recognition of the odorant by the lipid.[7] Significant chiral discrimination effects are observed in the isotherm and surface potentials of the carvone:DPPC system. Obviously, the chirality of the odorant and the lipid is playing a key role in the observed discrimination. However, the molecular study of the interaction between the chiral lipid and chiral odorant is unavailable, and the present study is aimed to be a pilot study in this direction.

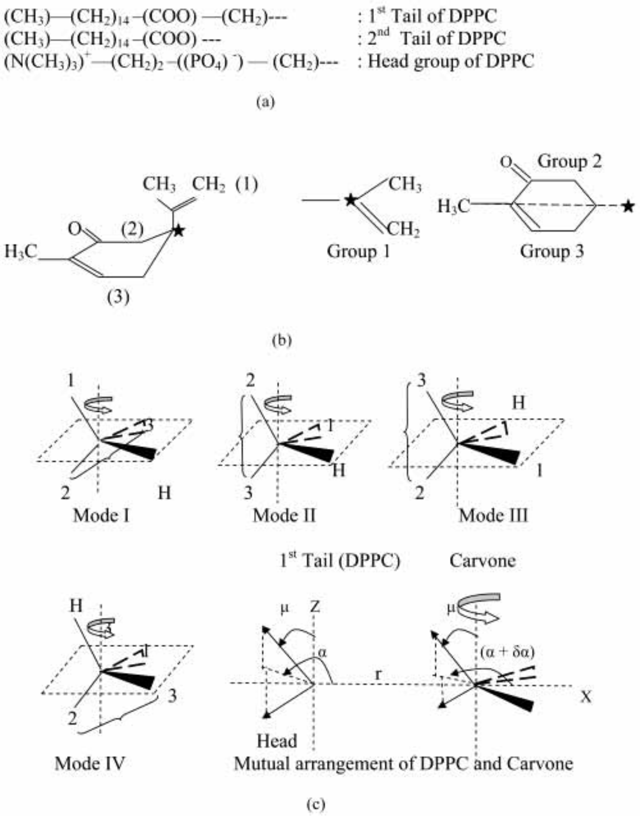

Figure 1. (a) Different segments of the molecular chiral structure of DPPC. (b) The representation of different groups (denoted as 1,2 and 3) of carvone used in calculation. (c) Different modes of orientation of the carvone molecule relative to DPPC considered in the present work. The second bracket indicates that groups 2 and 3 belong to the same cyclic structure. Also shown below is the mutual orientational arrangement of groups of carvone and DPPC for all modes in general. The angle μ indicates the tilt of the DPPC 1st tail (with respect to Z axis) and is parallel to the tilt of the group (or atom) of carvone directed toward air. The azimuthal projection of the DPPC 1st tail and headgroup is α, whereas the azimuthal projection of the adjacent group of carvone is $\alpha + \delta\alpha$. The $\delta\alpha$ is the mutual orientation between the pair of molecules and varied from 0° to 360° (anticlockwise with respect to X axis).

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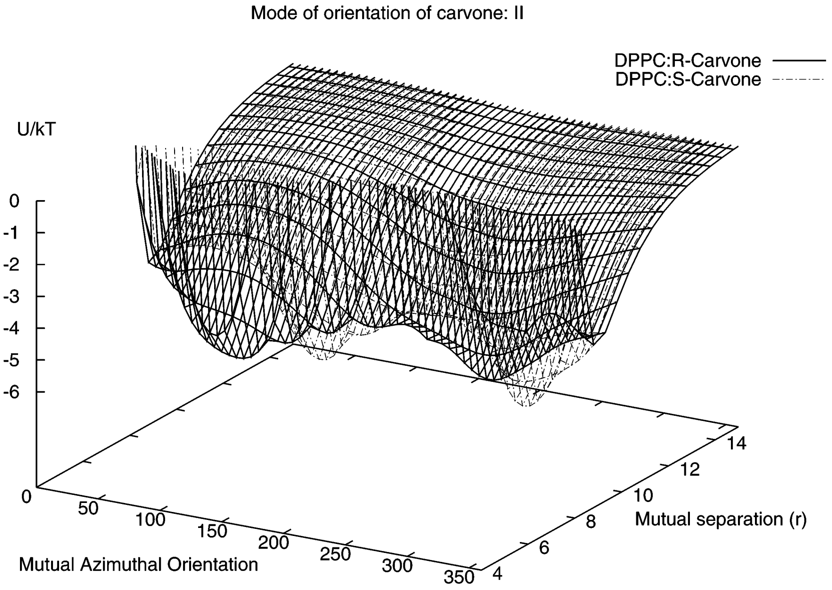

Figure 2. Comparison of the effective pair potentials of D-DPPC and *R*-carvone (indicated by solid lines) and D-DPPC and *S*-carvone (indicated by dot−dashed line) for mode II orientation of carvone (as shown in Figure 1). The temperature is 293.15 °K. The mutual orientation between the pair of molecules is expressed in degrees and varied from 0° to 360°. The intermolecular separation is expressed as *r*. Parameters necessary for calculation are shown in Table 1. The dielectric constant of the aqueous subphase is taken as 80.

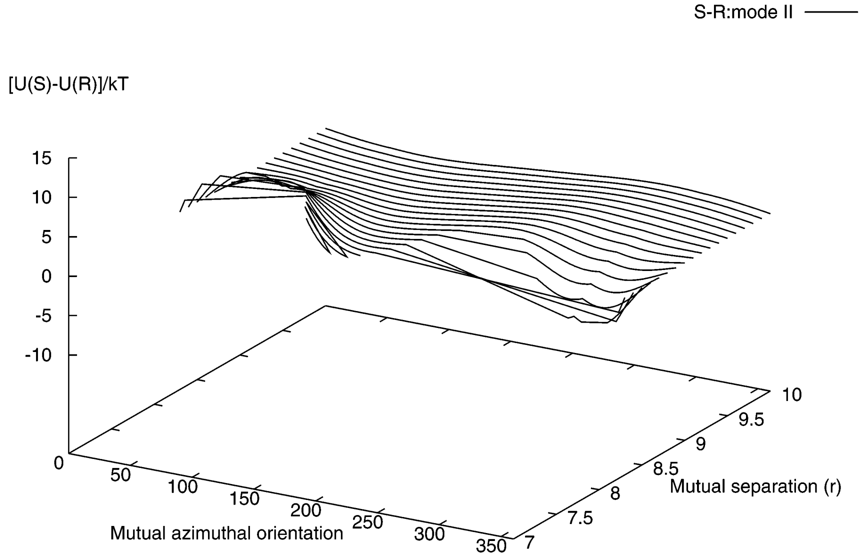

Figure 3. Values of ($\Delta U = (U(S\text{-carvone:D-DPPC}) - U(R\text{-carvone:D-DPPC}))/k_BT$) for mode II orientation of carvone. The range of $\Delta U/k_BT$ is +15 to −10. The mutual orientation between the pair of molecules is expressed in degrees and varied from 0° to 360°. The intermolecular separation is expressed as *r*. The variation in intermolecular separation is made up to 10 Å. Parameters necessary for calculations are shown in Table 1. Temperature is 293.15 °K.

In recent years, advances have been made in experimental[8] and theoretical studies based on EPP of chiral lipid monolayers.[9] In the present paper, we calculate the EPP profiles of *R*-carvone:D-DPPC and *S*-carvone:D-DPPC pairs to understand the chiral recognition.

2. Theoretical Calculation

The EPP is calculated by a Lennard-Jones (LJ) potential and dipolar interaction, as follows

$$U/k_BT = \sum_{\substack{g(i)\\g(j)}} (4/T)(\epsilon^{g(i)g(j)}/k_B)[(s^{g(i)g(j)}/\sigma^{g(i)g(j)})^{-12} - (s^{g(i)g(j)}/\sigma^{g(i)g(j)})^{-6}] + \sum_{\substack{g(i)\\g(j)}} (\mu_{g(i)}\mu_{g(j)}/4\pi\epsilon_s\epsilon_0(s^{g(i)g(j)})^3) \quad (1)$$

Here, $s^{g(i)g(j)}$ is the orientation dependent distance between the *g(i)* and *g(j)* groups,[9] $\sigma^{g(i)g(j)}$ is the average LJ diameter of the corresponding groups, and the energy parameter $\epsilon^{g(i)g(j)}$ is given by the Berthelot rule

$$\epsilon^{g(i)g(j)} = (\epsilon^{g(i)}\epsilon^{g(j)})^{1/2} \quad (2)$$

The dipole moments of DPPC is denoted by $\mu_{g(i)}$ (15.25 D[9e]). The dipole moment of carvone is recently calculated[10] using a standard molecular modeling technique with the help of a well-known quantum mechanical program package (CHEM 3D software),[11] and the theory used is at the semiempirical PM3 level.[12] The charges are obtained using the Mulliken population analysis (MPA) technique.[13] The calculated dipole moment of carvone is denoted as $\mu_{g(j)}$ (3.014 D). ϵ_0 is the vacuum permittivity. ϵ_s is the static dielectric constant, which has nontrivial position dependence.[14] We calculated EPP with

TABLE 1: Parameters Used for the Calculation of EPP of the Carvone−DPPC System[a]

molecule	group	σ	ϵ^g/k_B
DPPC	first tail	8.52	852
	head	7.20	720
carvone	1st group	4.51	451
	2nd group	4.50	450
	3rd group	4.33	433

[a] The temperature is 293.15 °K. The tilt and azimuthal orientation of the 1st tail of DPPC are 24.91° and 143°, respectively. The diameter, σ, is in Å, and ϵ^g/k_B is in °K.

TABLE 2: Results of the Calculation of Minimum of EPP (U_{min}) of the Enantiomeric Carvone and D-DPPC Pair Corresponding to the Modes Shown in Figure 1[a]

mode	enantiomer of carvone	U_{min} ($\epsilon_s = 80$)	U_{min} ($\epsilon_s = 40$)	U_{min} ($\epsilon_s = 10$)	U_{min} ($\epsilon_s = 5$)
I	*R*-	−5.86	−5.79	−5.35	−4.77
	S-	−5.94	−5.86	−5.37	−4.74
II	*R*-	−5.88	−5.84	−5.63	−5.36
	S-	−5.98	−5.95	−5.74	−5.47
III	*R*-	−5.96	−5.90	−5.69	−5.40
	S-	−5.95	−5.90	−5.57	−5.20
IV	*R*-	−4.85	−4.77	−4.29	−3.97
	S-	−4.78	−4.69	−4.37	−4.03

[a] ϵ_s stands for the dielectric constant of the aqueous subphase. The temperature is 293.15 °K. The parameters are shown in Table 1.

various values of ϵ_s. The molecular structures are considered based on equivalent sphere (ES) based representation described earlier,[9a,b,d,e] and the closest interactions between neighboring molecules (1st tail of DPPC and its head with the carvone molecule) are considered. The effective representation of dissymmetry of carvone and DPPC are shown in Figure 1, parts a and b, respectively. The dipole of carvone is assumed to be located on group 2 (see Figure 1a), where the maximum charge separation occurs. The average azimuthal orientation and tilt of D-DPPC are used from GIXD data.[15] The carvone molecule can orient in the aqueous subphase, and numerous variations of mutual orientations (relative to DPPC) are possible. We systematically select some specific modes of orientations of the carvone molecule with respect to DPPC, and they are shown in Figure 1c. The topmost group in each mode is assumed to have the same tilt as the DPPC 1st tail. The azimuthal orientation and separation of carvone and DPPC are varied to calculate EPP. The energy parameters and diameters of the groups are calculated as described previously using standard methods.[9] The parameters used in the calculation are presented in Table 1.

3. Results and Discussion

The discrimination of *R*-carvone:D-DPPC and *S*-carvone:D-DPPC systems is observed in the mutual orientation and distance dependence as well as minima (U_{min}) of EPP profiles for all modes and all values of ϵ_s as shown in Table 2. The ES representation is a minimal representation of the chirality of the molecule concerned,[9d] and hence, the observed discrimination is small. The EPP profiles for carvone−DPPC corresponding to mode II are shown in Figure 2 and are different from the EPP profile of pure DPPC. Out of four modes, the deepest energy minimum is observed in mode II because, with the dipoles being farthest, the electrical repulsion is least in this mode. Figure 2 shows that the lipid and odorant can have a strong favorable interaction only at a certain specific mutual orientation and separation determined by the chirality of the concerned molecules. Thus, the molecular origin of the chiral recognition of the odorant by the lipid is due to the molecular chiral structure and concomitant discrimination in EPP.

The discrimination is clear in Figure 3, where we plot the differences of EPP of enantiomeric pairs, i.e., [U(*S*-carvone: DPPC) − U(*R*-carvone:DPPC)] (denoted as ΔU) for mode II. Only negative values of EPP are used to calculate the ΔU because a stable mutual interaction between the odorant and DPPC is relevant. The periodic variation in ΔU is observed clearly indicating chiral discrimination, which vanishes at large separation as expected.

Thus, the present calculation shows that the carvone and DPPC may have an average preferred orientation relative to DPPC depending on the chirality of the concerned molecules. This conclusion corroborates the experimental conclusion that carvone may have a preferred average stereoselective orientation.[7] Table 2 shows that the D-DPPC molecule has the strongest favorable interaction with *S*-carvone (compared to *R*-carvone). Based on the mirror-image relationship of the spatial arrangement of the groups of chiral molecules, it is straightforward to conclude that the L-DPPC will have stronger interaction with *R*-carvone (compared to *S*-carvone). This conclusion is consistent with the experimental observation that the interaction of L-DPPC is stronger with *R*-carvone than *S*-carvone.[7]

The present calculation can be improved by considering the explicit molecular structure and charge distribution rather than the ES representation and point dipole approximation used here. More experimental studies, such as GIXD and Brewster angle microscopic studies, are required to understand the details of the microscopic and mesoscopic features of the odorant-lipid monolayer system. The understanding of the odorant−lipid interaction has immense biological (understanding the physiological process of odor perception) and technological significance (understanding the structure−activity relationship as applied to food and perfumery industry).

4. Conclusions

The orientation and distance dependence of the EPP of the enantiomeric carvone and DPPC are different for the enantiomers. The potential profiles are also different from the EPP of pure lipids. The average mode of orientation of carvone with less dipolar repulsion is found to give favorable interaction compared to other modes of orientation with greater dipolar repulsion from the present model. The present study shows that a stronger favorable interaction occurs between D-DPPC with *S*-carvone rather than with *R*-carvone. It is concluded based on the mirror-image relationship that a stronger favorable interaction occurs between L-DPPC with *R*-carvone rather than with *S*-carvone. This corroborates with the experimental result that *R*-carvone interacts strongly with L-DPPC. It is concluded that the differences in interaction due to the chirality of molecules play a significant role in the recognition of odorant by the lipid.

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