Molecular study of heterochiral preference in biomimetic monolayers

N. Nandi
Chemistry Department, Birla Institute of Technology and Science, Pilani 333 031, India

Heterochiral discrimination in Langmuir monolayers of amphiphilic 1-stearylamine-glycerol is studied theoretically using coarse-grained molecular model. The present study reveals different effective interactions for enantiomeric and racemic pairs of the 1-stearylamine-glycerol amphiphile. The study conclusively shows that the chiral structure of the molecule and the lattice packing drive the chiral preference at the mesoscopic level. Besides justifying the experimentally observed handedness of the filigree-shaped domains, the theoretical results explain the experimentally observed heterochiral discrimination.

Chirality is present at all levels of structural hierarchy of biological molecules such as proteins, nucleic acids and lipids, and dictates their functionality. Why Nature is so specific about chirality is posing the famous question regarding the origin of homochiral evolution. Due to the fundamental importance of understanding the chirality-dependent interactions in biomolecular assemblies, monolayers are used as simpler biomimetic systems. Effects of chirality manifest in monolayers in various ways. The shape of the mesoscopic condensed-phase domains formed in monolayers could be anisotropic and hence chiral. The underlying lattice structure in these monolayers could also be chiral. Two types of interactions can occur at the molecular level in such systems. The D–D (or L–L) interaction could be favoured over D–L interaction (homochiral interaction), or the D–L interaction could be more (or D–D) interaction (heterochiral interaction). Both homochiral and heterochiral interactions are observed in Langmuir monolayers. Thus, the monolayers provide a unique opportunity to understand the chiral preference as mimetic systems.

Interesting filigree-shaped domains are observed using fluorescence microscopic studies of the condensed monolayer phase of 1-stearylamine-glycerol. The filigree domains of the R(+) enantiomers are curved clockwise, whereas those of S(−) enantiomers are curved anticlockwise, whereas the domains of the racemic mixtures are curved without a specific sense of direction. The enantiomeric lattice is oblique, whereas the racemic lattice is rectangular-centred, as found by Grazing Incidence X-ray Diffraction (GIXD).

In the present study, the heterochiral discrimination in 1-stearylamine-glycerol monolayers is investigated using a coarse-grained molecular model based on an effective pair potential (EPP) based theory. The EPP between the \( i \)th and \( j \)th molecules in a monolayer, each of which is composed of several groups (indicated by \( g(i) \) or \( g(j) \)), such as CH\(_3\), CH\(_2\), NH and OH, is calculated using a Lennard–Jones pair potential given by the form

\[
\frac{U}{k_B T} = \sum_{g(i),g(j)} 4\epsilon \frac{g(i)g(j)}{k_B T} \left[ \frac{\sigma g(i)g(j)}{\sigma g(i)g(j)} \right]^{-12} - \left( \frac{\sigma g(i)g(j)}{\sigma g(i)g(j)} \right)^{-6}.
\]

Here, \( \epsilon \) is the orientation-dependent separation between interacting groups. The energy parameter is calculated by the Berthelot rule, \( \epsilon = \sqrt{\epsilon_{g(i)}\epsilon_{g(j)}} \) and \( \sigma = \sigma_{g(i)}\sigma_{g(j)} \) is the average diameter. Temperature is 293.15 K in all cases (Table 1).

The \( (\epsilon/k_B) \) parameter for the CH\(_3\), CH\(_2\) and CH groups is taken from the available data given in OPLS. The data for N and O are used to represent the NH and OH groups, because H has zero energy in the Optimized Potential for Liquid Simulations (OPLS) set. The effective diameters of the groups are calculated from the group increment data tabulated by Bondi, and using the empirical relations provided by Ben Amotz and Herschbach. Andelman and Orland have also used representative values of parameters in the study of the chiral discrimination. It may be noted that exact magnitude of the energy parameter has no crucial bearing on the investigated monolayer features such as handedness or discrimination energy, as discussed earlier.

In calculating the EPP, the neighbouring molecule is rotated anticlockwise in the interfacial plane and simultaneously the distance between the pair of molecules is gradually changed. The pair potential is calculated at each position of the mutually oriented state of the pair of molecules. The tilt of the head groups in the aqueous subphase is unknown. Thus, the EPP of the head group is calculated as a function of three variables; first, the separation of neighbouring head groups, second, the orientation of the head group from the normal (denoted by \( \beta \) and varied by 180°), and third, the mutual orientation of the neighbouring head groups (denoted by \( \delta_{\text{head}} \) and varied by 360°). The \( \beta \) value corresponding to the energy minimum is used to obtain the EPP of the head group as a function of mutual separation and \( \delta_{\text{head}} \).

The EPP for the alkyl tail part of the enantiomeric \( S(−) \)-1-stearylamine-glycerol is shown in Figure 1a. The notable feature of the EPP plots is the deepest minimum at 15°.

### Table 1. Parameters for calculation of EPP of 1-stearylamine-glycerol

<table>
<thead>
<tr>
<th>Group</th>
<th>( \sigma (\text{Å}) )</th>
<th>( \epsilon/k_B (\text{K}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)</td>
<td>2.99</td>
<td>80.50</td>
</tr>
<tr>
<td>CH(_2)</td>
<td>2.45</td>
<td>59.37</td>
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<tr>
<td>CH</td>
<td>1.40</td>
<td>40.25</td>
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<tr>
<td>OH</td>
<td>2.96</td>
<td>105.66</td>
</tr>
<tr>
<td>NH</td>
<td>3.25</td>
<td>85.53</td>
</tr>
</tbody>
</table>

e-mail: nnandi@bits-pilani.ac.in

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mutual orientation for the enantiomeric pair. The potential well of the head group segment (Figure 1 b) is complex due to the presence of different groups present in the head region. The total intermolecular pair potential is largely governed by the tail-pair interaction compared to the head-group-pair interaction due to deeper potential well of the former pair. The 15° mutual orientation indicates that with respect to the tail of a reference molecule, the neighbouring tail (placed progressively away from the eye) of another molecule will be rotated 15° anticlockwise. Consequently, the handedness of $S(-)-1$-stearylamine-glycerol would be anticlockwise. This is in agreement with the experimentally observed handedness.$^{10}$

The EPP of the tail part of the racemic pair is shown in Figure 2 a. The profile is completely different as well as deeper compared to the enantiomeric pair potential. It has a broad minimum, without any significant orientation dependence. The potential well of the tail–tail EPP is deeper than the EPP minimum of the corresponding head-group segment (Figure 2 b). The head-group profile is complex due to different groups present in the head-group region, as indicated earlier and is also different from the head–
head interaction of the enantiomeric pair. Consequently, the total intermolecular pair potential for the racemic pair would be orientation-independent, and it is expected that there would be no preferential mutual orientation of tails of the racemic pair. This is consistent with the experimental observation that the racemic mixture forms fractal domains without any specific curvature. The deeper EPP of the racemic pair compared to the enantiomeric pair indicates strong heterochiral preference, as observed experimentally. This explains why chiral segregation is not observed in the racemic 1-stearylamine-glycerol.

Thus, the experimentally observed handedness of the enantiomeric pair as well as the irregular domain shape of the racemic pair can be explained from the present molecular model. Use of experimental information about tilt and azimuthal projection as well as the average molecular structure is responsible for the observed agreement between theory and experiment. It may be noted that the experimentally observed tilt and azimuthal projection are the outcome of interaction of the concerned molecule with the neighbouring molecules, as well as interaction of the molecules in aqueous subphase. Thus, the inclusion of
the structural information via the GIXD data effectively incorporates these interactions and leads to a correct prediction of the mesoscopic properties, such as the handedness and heterochiral discrimination in the curvature of the filigree domain structures.

It may be noted that the manifestation of chiral discrimination is rather subtle, as recently reviewed. In some cases the EPP profiles of enantiomeric and racemic pairs are not different overall and they also have similar domain shape. However, the precise orientation and distance dependence of EPP may be different and lead to chiral discrimination. Recently, domains of 1-O-alkyl glycerol amphiphiles were studied. The depth of minima and the overall shapes of the pair-potential profiles of tail and head parts of S-enantiomeric and racemic 1-O-hexadecyl glycerol are rather similar. It is observed that the overall shapes of enantiomeric and racemic pairs are apparently similar. The isotherms as well as the fluorescence images of enantiomeric and racemic 3-hexadecyl-oxy-propane-1,2 diol (HOPD) are also similar. However, the orientation and distance dependence are rather different in the two cases. Explicitly, the global minima, global maxima and saddle points are located at different mutual separation and orientation for the enantiomeric pair and racemic pair. A cross-over between homo- and heterochirality exists. This cross-over is supported by experimental data. Thus, apparently similar looking EPP profiles can have subtle differences and may lead to significant discrimination.

Summarizing, the study revealed different effective interactions for enantiomeric and racemic pairs of 1-stearylamine-glycerol amphiphile. It is shown that the molecular structure (explicitly, chemical composition and spatial arrangement of atoms or groups) and the packing of molecules in the two-dimensional lattice dictate chiral preference. Information gained from the present study indicates that it is possible to carry out similar molecular studies in related three-dimensional biological chiral systems (with consideration of one more degree of freedom) to understand the chiral preference in these systems. This will be an important future problem to study.


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