Comparison of the Intermolecular Energy Surfaces of Amino Acids: Orientation-Dependent Chiral Discrimination

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In the present work, we compare the intermolecular energy surfaces of the alanine molecule in its neutral and zwitterionic state using ab initio theory (HF/6-311++G**) as a function of mutual orientation. Starting from the optimized structures of the nonbonded homochiral (L−L) and heterochiral (D−L) pairs of molecules, the energy surfaces are studied with rigid geometry by varying the distance and orientation. The potential energy surfaces of the L−L and D−L pairs are found to be dissimilar and reflect the underlying chirality of the homochiral pair and racemic nature of the heterochiral pair. The intermolecular energy surface of the L−L pair is more favorable than the corresponding energy surface of the D−L pair. The study, for the first time, reveals clear homochiral preference without use of parameters, which was unobserved in previous detailed simulations but predicted by theory. The electrostatic interaction further augments the chiral discrimination. The basis set superposition error (BSSE) corrected results show enhanced discrimination. Use of higher-level Møller-Plesset perturbation theory (MP2) and further BSSE correction do not change the conclusions made at the Hartree−Fock (HF) level. The major conclusions based on HF and MP2 level calculations remain unaltered when the calculations of the potential energy surfaces for the neutral and zwitterionic pairs are repeated using the density functional theory (DFT) (B3LYP/6-311++G**). The observed orientation dependence has significance in the biological chiral recognition as well as peptide synthesis at the peptidyl transferase center where the amino terminal and peptidyl terminal undergo mutual rotatory motion.

I. Introduction

Orientation dependence of the intermolecular interaction is important in the biomolecular or biomimetic systems where molecular chirality is involved. The consideration of the orientation-dependent molecular interaction energy profile is found to be useful in understanding the higher-level structure of the mesoscopic aggregates of biomimetic lipids, peptides, and their recognition events.[1−6] Mesoscopic structure formation occurs with the favorable intermolecular orientations between concerned molecules in the condensed phase. Similarly, the feasibility of the intermolecular recognition depends on the stability of different intermolecular arrangements as a function of mutual orientation and distance. In general, exploration of the intermolecular energy surface is useful in understanding many biochemical phenomena including chiral discrimination.[4] Chiral discrimination is a rather broad term encompassing various manifestations of the properties of chiral systems.[1] For example, the differences between the absolute energies of L- and D-isomers (a negligibly small energy difference)[7,8] as well as the differences between L−L and D−L intermolecular energies as a function of separation (a small but nonnegligible energy difference as a function of distance and a significant energy difference as a function of mutual orientation)[4,9,10] are studied as chiral discrimination. Similarly, the experimentally observed different macroscopic (major differences in isotherm features), mesoscopic (significantly different shapes or handedness of domains composed of pure enantiomeric (L−L or D−D) or racemic (D−L) systems), or microscopic (significant measurable differences in lattice structures of enantiomeric or racemic molecular aggregates) features are also termed as chiral discrimination.[1] We aim to investigate the differences in the nature of discrimination of the features of the intermolecular energy surfaces of pure (L−L) and racemic (D−L) molecular pairs as a function of orientation using electronic structure based calculations (ab initio and density functional theory (DFT)) in the present work.

The understanding of the intermolecular interaction between chiral molecules also has relevance to the related problems of biological chirality and chiral recognition processes. The phenomenon that all living organisms use one enantiomer of the different biological molecules (amino acids, carbohydrates, steroids, and lipids) exclusively or sometimes in great excess is called "biological chirality" and is a subject of intense research.[11a−f] The orientation dependence of the intermolecular interactions is expected to play an important role in biomolecules, which express chirality at different levels of structural hierarchy. Also, the recognition process is essentially dependent on molecular interactions. Chiral recognition is a molecular recognition process in which one enantiomer of a molecule preferentially interacts with one enantiomer of (usually) a second substance.[12a−g] Chiral recognition is relevant in biological systems because biological receptors are able to recognize enantiomeric molecules such as odorants[13a−g] and drugs.[13h] Orientation-dependent molecular interaction between the receptor and the ligand molecule will determine the strength of the binding between the two species and how effective is the recognition.

Chiral discrimination also plays an important role in many biological processes crucial for life. Peptide biosynthesis is an important reaction where the orientation between the participat-

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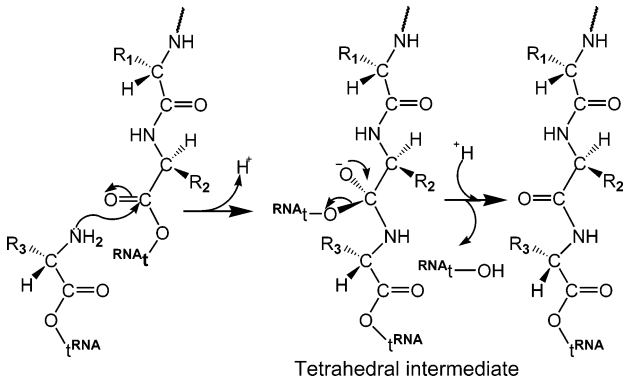

Figure 1. Schematic representation of the peptide bond formation at the peptidyl transferase center via tetrahedral intermediate.[14]

ing molecules is known to be important. In this process, the α-amino group of the amino acyl-tRNA at the A-site makes a nucleophilic attack at the carbonyl carbon of the ester bond of the peptidyl-tRNA at the P-site and forms an intermediate, which subsequently generates the peptide bond and the polypeptide chain length grows (see Figure 1).[14] The 3′ end of the A-site arrives at the P-site by a process of mutual rotation between them.[15] Thus, the intermolecular energy profile of the A-site and P-site is expected to be orientation dependent, and with these two ends being chiral, their chirality might influence the nature of the energy surface. The question of whether chirality of the A-site and P-site influences the orientation dependence of the interaction energy profile of the molecular segments representing an amino acid attached to the respective sites is related to the question of biological selection of the L-enantiomer over the D-enantiomer.

D-Amino acid is isolated from amphibians and other invertebrate species such as snails, cray fish, and lobster. However, the enzymatic actions of such peptides containing D-amino acids are very different from the natural peptides containing only L-amino acid.[16,17] D-Alanine and D-glutamyl residues are observed in the cell wall of bacteria. D-Valine and D-phenylalanine are present in many antibiotics including valinomycine, actinomycine, gramicidin S, and tyrocidines.[18a] They are synthesized by nonribosomal pathways and through multienzyme systems like racemase and amino acid transferase in microorganisms. D-Amino acid is found in higher organisms as free, peptide, and protein-bound D-amino acids. The function of D-amino acid in protein may presumably be related to the process of aging.[18b] It is a puzzle that, despite identical physical properties (except a chirality-dependent property, such as optical rotation) and nearly identical energy of the two enantiomers at the respective optimized conformational states (difference is rather small compared with the thermal energy, k_BT), they are easily and accurately discriminated by biological organisms. Although tRNA normally carries L-amino acids, the minute presence of D-amino acid can lead to mistake which will result in diminished or changed biological activity. Ribosomes can exclusively accept the L-isomer and accurately reject the D-isomer, which is a surprising choice. It is an open question of how the L-isomer of amino acid is exclusively accepted over the D-isomer at the peptidyl transferease center.

The rotatory motion leads to orientation dependence of the interaction energy of the A-terminal with the P-terminal. If the energy profile of the L−L pair is more favorable than the D−L pair in the span of orientations covered in rotatory motion, then the favorable selection of the L-isomer can be understood. However, to the best of our knowledge, no quantitative calculation about the energy profile related to the A-to-P rotatory process is available at present. Structural analysis suggests that either the steric hindrance of the molecular segments of D-amino acid or the improper orientation for the nucleophilic attack by the amino group could lead to unfavorable incorporation of D-isomer.[15] However, this issue is not addressed quantitatively. Consequently, it seems that the study of the orientation-dependent energy surfaces of chiral and achiral amino acids could be useful to understand the chiral preference of A-site and P-site interaction. Since the energies of L- and D- molecules themselves at their optimized geometries differ only insignificantly, it is unexpected that the interaction energy between L−L and D−L pairs would differ significantly at the optimum geometry of the pair at the corresponding mutual orientation and separation between the molecules. This is also observed in earlier studies.[9,10] However, it is unknown at present whether the same conclusion holds or not when the intermolecular orientation at the given distance between the molecules will be different from that corresponding to the optimized geometry of the pair of molecules. It is possible that the interaction energy between L−L and D−L pairs might vary as a function of orientation (while each molecule may retain their optimized conformation). Since it is obvious that the pair of enantiomers during the A-to-P rotatory process will deviate from their optimized pair geometry and should go via several different mutual intermolecular orientations and distances, it is useful to look into the corresponding orientation dependence of the energy profiles. If a given pair of molecules (say, L−L) can undergo through a lower-energy pathway during the process of mutual rotation, then the corresponding pair interaction is expected to be more favorable than that of the other pair (namely, that of the D−L pair).

It may be noted that detailed and accurate information of the orientation dependence of the interaction energy for simple molecules is a challenging problem.[19] The study of the orientation dependence of the energy profile of interaction of chiral molecules is even more difficult due to the subtle nature of discrimination. Extensive Monte Carlo simulation of alanine could not reveal the discrimination beyond the stochastic error limit.[9,10] On the other hand, experiment, model calculations, and pair potential theories indicated that chiral discrimination could be observable for larger molecules for which the effect is sizable.[1,4]

With this end in view, we performed a detailed potential energy surface scan of the neutral and zwitterionic L−L and D−L alanine as a function of orientation and distance between the molecules using ab initio theory at the Hartree−Fock (HF) level with a reasonably large basis set (6-311++G**). We also scanned the energy profile of a pair of glycine molecules as an example of an achiral molecule. The discrimination between the energy profiles of L−L and D−L pairs is calculated for neutral and zwitterionic species. The possible error due to basis set superposition error (BSSE) is corrected. The orientation-dependent discrimination energy is recalculated with higher-level theory (Møller−Plesset second-order perturbation theory (MP2)), and the BSSE is further corrected at the later level. Our results unambiguously show that the orientation-dependent energy profiles of L−L and D−L alanine molecular pairs are not identical. The L−L interaction is relatively more favorable than the D−L interaction in the orientational space. This indicates a chiral discrimination with homochiral preference. The discrimination is highly significant at orientations where the neighboring molecular segments come in steric hindrance with variation in mutual molecular orientation.

To compare the results of the calculations based on the HF level or MP2 level with other theoretical approaches, we recalculated the interaction energy profiles between L−L and D−L pairs of both neutral and zwitterionic alanine molecules using DFT. The Becke three-parameter Lee−Yang−Parr (B3LYP) functional and 6-311++G** basis set are used in the present work, and the geometry is optimized at the same level of theory and basis set. It needs to be pointed out that the stable zwitterionic form of the amino acid could not be obtained using DFT.[20a−d] The zwitterionic species can be stabilized by incorporation of solvation effect.[20e] However, in the present work where a pair of zwitterionic alanine molecules are considered, a given zwitterionic alanine molecule does not convert into neutral species due to the presence of the carboxyl group of the neighboring molecule in the proximity of the proton attached to the amine group of a given alanine molecule. This is further discussed in the Results and Discussion section. Besides, there are other reported limitations of the DFT in calculating the intermolecular interactions in general. It is known that, since the functional form of exact exchange-correlation energy is not known, current DFT methods cannot yield exact results. The lack of a systematic way to approach the exact result using a series of calculations is pointed out to be the deficiency of DFT methods. Also the theory does not allow an evaluation in the errors for a calculation when the results converge with the increase in basis sets, and the quality of a result can only be verified by comparing with the experimental result or with a high-quality wave mechanical result.[21] Despite these limitations, a number of successful DFT studies on the calculation of intermolecular interaction are also reported.[22a−e] It is further pointed out that the cost of DFT calculations is only N^3, where N is the number of basis sets, while the same for MP2 and MP4 are N^5 and N^7, respectively. Also, gradient-corrected results are either close or in some cases better than HF or MP2 results.[23] Thus, we also performed DFT calculations for the orientation dependence of interaction in the present work, in addition to the ab initio calculations (HF and MP2). The results of the DFT calculations are described in the Results and Discussion section.

The present study indicates that the steric hindrance between the amino acids themselves is an important source of discrimination, which is a new result. In the context of in vivo peptide synthesis, where the mutual interaction of A and P due to rotation is known to be stereospecific, the present result shows that the mutual steric hindrance of groups attached to the chiral center is important for homochiral preference. The presence of electrostatic interaction further enhances the homochiral preference. The results are free of parameters and not sensitive to the use of basis sets. We believe that this is the first demonstration of homochiral discrimination of the smallest chiral amino acid (alanine). The organization of the rest of the paper is as follows. We present the theoretical calculation in the next section (section II), which is followed by results and discussion (section III).

II. Theoretical Calculation

At first, pairs of L−L and D−L alanine molecules are energy optimized in their neutral state at the HF/6-311++G** level of theory. The Cartesian coordinates of the atoms of the pair of the neutral pair of L−L and D−L alanine molecules at the HF level of theory are given in Table 1 of the Supporting Information. The potential energy surface is scanned as a function of distance and orientation starting from the optimized geometry (with rigid geometry) as described below. The distance between the nitrogen atom of the amino terminal of one amino acid molecule and the oxygen atom of the carboxyl group of the other amino acid molecule is increased (the respective atom pairs are not covalently bonded) keeping one molecule as reference (shown schematically in Figure 2). At each point, the $C^{\alpha}-C'-O'\cdots N$ (the dotted line indicates that the respective atoms are not covalently bonded) dihedral angle is varied by 2π (note that the charge of the COO^- group is distributed over both oxygen atoms in the zwitterionic structure and the oxygen atom in the $C^{\alpha}-C'-O'\cdots N$ dihedral angle could be denoted as O″ as well[24]). The dihedral angle observed at optimized geometry is defined as the starting point (0°) of dihedral angle variation. The justification of such variation is that the peptide bond formation is possible only when the corresponding $-NH_2$ group of the amino terminal is in the proper orientation suitable for the nucleophilic attack at the carbonyl carbon of the carboxyl group. As the orientation dependence of the proximity effect of the peptide bond formation is important, the variation in energy of the L−L and D−L pairs with the dihedral angle will reveal the chiral discrimination of the corresponding pairs. The resulting energy profile is expected to provide information about the energetic advantage (if any) of the approach of an L-alanine (with varying orientation and distance) to another L-alanine compared with the corresponding process where a D-alanine molecule approaches the L-alanine molecule. Specifically, the $2C^{\alpha}-3C'-6O'\cdots 14N$ dihedral angle for the neutral L−L pair of molecules and the $1C^{\alpha}-2C'-4O'\cdots 7N$ dihedral angle for the neutral D−L pair of molecules are varied (see Figure 2).

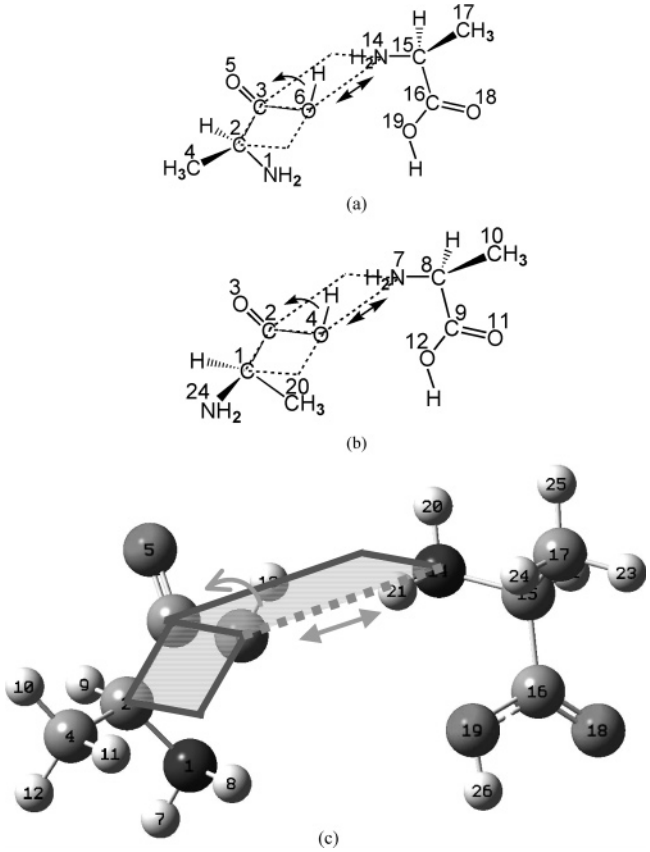

Figure 2. (a) Mutual dihedral angle variation in a pair of nonbonded neutral L−L alanine molecules, (b) the mutual dihedral angle variation in a pair of nonbonded neutral D−L alanine molecules, and (c) the mutual dihedral angle variation in a pair of nonbonded neutral L−L alanine molecules, same as those in part (a), showing the planes related to the variation of the dihedral angle and the distance related to the variable intermolecular separation indicated by the dotted line.

A pair of zwitterionic L−L and D−L alanine molecules are also energy optimized at the HF/6-311++G** level of theory. The Cartesian coordinates of the atoms of the pair of the

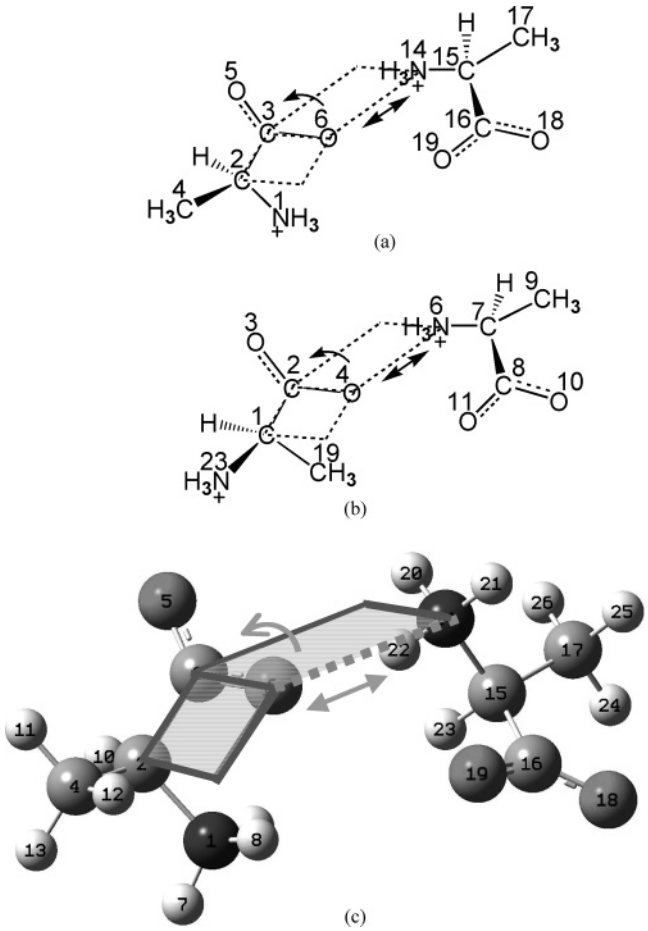

Figure 3. (a) Mutual dihedral angle variation in a pair of nonbonded zwitterionic L−L alanine molecules, (b) the mutual dihedral angle variation in a pair of nonbonded zwitterionic D−L alanine molecules, and (c) the mutual dihedral angle variation in a pair of nonbonded zwitterionic L−L alanine molecules, same as those in part (a), showing the planes related to the variation of the dihedral angle and the distance related to the variable intermolecular separation indicated by the dotted line.

zwitterionic pair of L−L and D−L alanine molecules at the HF level of theory are given in Table 2 of the Supporting Information. The potential energy surface for the pair of molecules is investigated as a function of distance and orientation starting from the respective optimized geometry as described before for the neutral state. The $2C^{\alpha}-3C'-6O'\cdots14N$ dihedral angle for the zwitterionic L−L pair of molecules and the $1C^{\alpha}-2C'-4O'\cdots6N$ dihedral angle for the zwitterionic D−L pair of molecules are varied (see Figure 3).

The energy difference between the L−L-pair and D−L-pair at a given intermolecular orientation and separation for the same value of both variables for both pairs is defined as the chiral discrimination energy and is denoted by ΔE_{LL-DL}. The difference in the nature of the energy surfaces of the respective pairs can be understood from ΔE_{LL-DL} as a function of orientation. The sign of ΔE_{LL-DL} will indicate homochiral (ΔE_{LL-DL} is negative) or heterochiral (ΔE_{LL-DL} is positive) preference. In case ΔE_{LL-DL} is negative, it will indicate that the L−L interaction is more favorable at that intermolecular orientation and distance than the corresponding D−L interaction at the same mutual orientation and distance between the molecules. When the sign of the calculated ΔE_{LL-DL} is negative, we indicate the discrimination energy as $\Delta E_{LL-DL}^{Homochiral}$, and when the calculated ΔE_{LL-DL} is positive, we indicate the same as $\Delta E_{LL-DL}^{Heterochiral}$. Only negative and stable conformational energies of the L−L pair as well as the D−L pair are observed in the individual energy plots of the L−L pair and D−L pair, and these values are used in calculating the discrimination because stable energies are relevant to reactant geometry in peptide bond formation. The discrimination is computed for both the neutral and zwitterionic states. It is well-known that BSSE gives rise to artificial lowering in energy in the computation of intermolecular interaction.[25] We carried out further calculations to ensure that the discrimination observed is not artificially generated by BSSE. At first, BSSE is corrected by the counterpoise method at the same level of theory (HF/6-311++G**) in the region in which the maximal $\Delta E_{LL-DL}^{Homochiral}$ and $\Delta E_{LL-DL}^{Heterochiral}$ values are observed in the potential energy profile. Subsequently, the same points in the energy surface are again calculated by the MP2/6-311++G** level of theory. HF theory treats the correlation between the motions of the electrons within a molecular system inadequately. MP2 theory attempts to incorporate electron correlation by adding higher excitations to the HF theory as a noniterative correction. In the present calculation, BSSE is further corrected at the same (MP2/6-311++G**) level using the counterpoise method. The energy profile of the naturally available achiral amino acid, glycine in the zwitterionic state, is also investigated to better compare the effect of chirality of alanine. The orientation and distance dependence is investigated as described before for alanine.

Pairs of L−L and D−L alanine molecules are energy optimized in their neutral as well as in their zwitterionic state using DFT by the B3LYP/6-311++G** level of theory. The Cartesian coordinates of the atoms of the pairs of neutral and zwitterionic L−L and D−L alanine molecules at the DFT level of theory are given in Tables 3 and 4, respectively, in the Supporting Information. As discussed earlier, the zwitterionic structure of single alanine molecule is unstable and the structure changes to a neutral alanine molecule. For a pair of zwitterionic alanine molecules as considered in the present calculation, a given zwitterionic alanine molecule does not convert into neutral species due to the presence of the carboxyl group of the neighboring molecule in the proximity of the proton attached to the amine group of the first alanine molecule. However, the position of the protons and charges over atoms should be considered in such calculations because those factors affect the energy of the pair of molecules as well as the geometry as discussed in the following section. The potential energy surface is scanned as a function of distance and orientation starting from the optimized geometry (with rigid geometry) in DFT calculations similar to that carried out in the ab initio calculations. All calculations are performed using *Gaussian 03W* suite of programs.[26] The results are presented in the next section.

III. Results and Discussion

The energy profiles of the L−L and D−L pairs of neutral alanine are shown in Figure 4 as a function of distance and orientation with variation in the $C^{\alpha}-C'-O'\cdots N$ dihedral angle (see Theoretical Calculation section for details). The plot shows that the interaction energy of the L−L pair and the corresponding interaction energy of the D−L pair are not identical neither with the variation of the distance and nor with the variation of the mutual orientation of two molecules. We would like to note that the conformational energy differences between the D or L molecules themselves are negligibly small (the energies are identical for their optimized structures) and the observed difference in the intermolecular potential is not due to any conformational difference. The conformational energies of L-alanine, D-alanine, the pair of L−L alanine, and the pair of

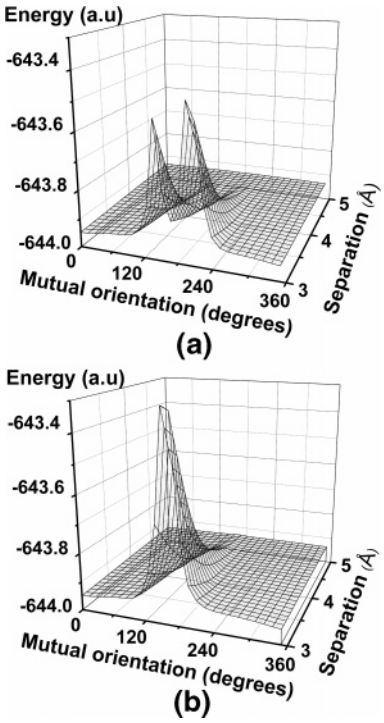

Figure 4. (a) Ab initio (HF/6-311++G**) potential energy surface of a pair of neutral L−L alanine molecules as a function of orientation (as shown in Figure 2a) and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair, and (b) the ab initio (HF/6-311++G**) potential energy surface of a pair of neutral D−L alanine molecules as a function of orientation (as shown in Figure 2b) and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair.

D−L alanine molecules in the neutral and zwitterionic state at their respective optimized geometries are given in Table 5 of the Supporting Information. The deviation in energies for the zwitterionic case between the L−L pair and D−L pair is due to the difference in the position of the proton between the amide groups and carboxyl group in the respective cases. The difference in the Coulombic interaction (considered using the partial charges over the proton and the neighboring oxygen as well as the corresponding separations in the L−L and D−L zwitterionic pairs in a vacuum), about 1 kcal/mol difference in energy, can be accounted. Considering the total energy in the hydrogen-bonded pair, one can understand the differences in the L−L and D−L pairs as observed in both theoretical methods. However, the conformational energy difference is rather small in view of the observed larger orientation-dependent discrimination as discussed in the following subsections. The plot of the L−L pair is dissymmetric revealing the underlying chirality of the molecules. In contrary, the plot for the D−L pair is symmetric around 180° orientation, which reveals the racemic state of the neutral pair. Both plots show gradually diminishing interaction when the molecules are far separated.

The orientational space for favorable L−L interaction is more specific than the corresponding space for the D−L pair. The plot of $\Delta E_{\mathrm{LL-DL}}$ with variation in the $C^{\alpha}-C'-O'\cdots N$ dihedral angle at given distances is shown in Figure 5 for neutral alanine pairs. The plot indicates that L−L interaction is more favorable in the complete range of orientation due to the maximum homochiral discrimination observed around 160° relative to the corresponding dihedral angle at optimized geometry (see the Supporting Information for the optimized geometry of the corresponding pairs). The relatively smaller magnitude of $\Delta E_{\mathrm{LL-DL}}^{\mathrm{Heterochiral}}$ is observed close to the range of orientation

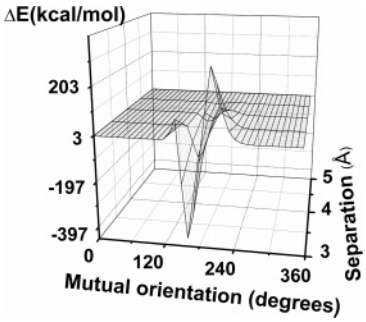

Figure 5. Chiral discrimination energy ($\Delta E_{\mathrm{LL-DL}}$) calculated from the ab initio (HF/6-311++G**) potential energy surface of pairs of neutral L−L and D−L alanine molecules as shown in Figure 4 as a function of orientation and distance.

at which the $\Delta E_{\mathrm{LL-DL}}^{\mathrm{Homochiral}}$ is significantly large. This can be understood from the fact that, at close to 160° relative orientation, the hydrogen atom of the methyl group of D-alanine is in steric hindrance with the hydrogen atom of the amino group of L-alanine. A rise in energy due to short-range steric repulsion is higher in the D−L pair than the corresponding rise in the L−L pair as can be observed from Figure 4. The interaction energy is lowered between the peaks of energy corresponding to a rise in steric repulsion in the case of the L−L pair and is not observed in the case of the D−L pair. As a result, the L−L pair shows a larger $\Delta E_{\mathrm{LL-DL}}^{\mathrm{Homochiral}}$ between the range of orientations, which exhibits hetereochiral preference ($\Delta E_{\mathrm{LL-DL}}$ corresponds to $\Delta E_{\mathrm{LL-DL}}^{\mathrm{Heterochiral}}$). Another reason for the observed preferred strong homochirality, albeit minor, could be that the second amino group (which is not involved in the dihedral angle of rotation) is more away from other groups in the D−L pair compared with the distance of the same in the L−L pair leading to the diminished nonbonded van der Waals interaction in the case of the D−L pair. In brief, the short-range steric interaction is less repulsive in the case of the L−L pair than the D−L pair, making $\Delta E_{\mathrm{LL-DL}}$ negative (corresponds to $\Delta E_{\mathrm{LL-DL}}^{\mathrm{Homochiral}}$). To the best of our knowledge, this is the first demonstration of the orientation-dependent chiral discrimination of an amino acid without the use of parameters in theoretical calculation.

It is pointed out that the very large difference between the energy surfaces of the L−L and D−L pairs at specific orientations at the same distances between corresponding pairs is due to short-range repulsive interactions (more specifically, due to a different distance dependence of the same for the L−L and the D−L pairs). In general, the short-range repulsive part of both van der Waals and electrostatic (Coulombic, dipolar, or multipolar) interactions varies more sharply than the corresponding long-range attractive part of the intermolecular interaction.[27a,b] The energy profile of L−L at a given short-range separation is less unfavorable than the corresponding energy profile of the D−L pair at the same intermolecular separation. However, the energy changes over a small separation distance are large at such a short-range intermolecular distance, and this causes the large discrimination observed.

Figure 5 shows that the energies of the L−L and D−L interactions at the same optimum separation are not identical as a function of orientation. Also it shows that the energy surface of the L−L interaction is more favorable *relative to* the D−L interaction in the overall range of mutual orientations possible. The Boltzman weighted averaging of $\Delta E_{\mathrm{LL-DL}}$ over the whole range of orientation also indicates the predominance of $\Delta E_{\mathrm{LL-DL}}^{\mathrm{Homochiral}}$. We would like to mention that since the L−L pair and D−L pair have different structures, the comparative ease of the L−L interaction can be shown in many different

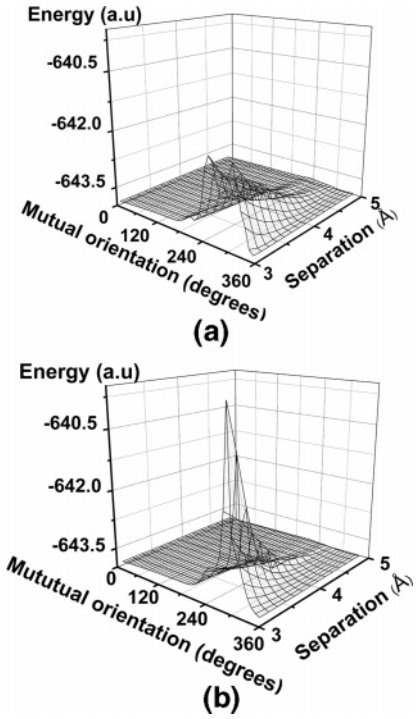

Figure 6. (a) Ab initio (HF/6-311++G**) potential energy surface of a pair of zwitterionic L−L alanine molecules as a function of orientation (as shown in Figure 3a) and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair, and (b) the ab initio (HF/6-311++G**) potential energy surface of a pair of zwitterionic D−L alanine molecules as a function of orientation (as shown in Figure 3b) and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair.

ways and the mapping of the two potential surfaces (L−L and D−L) can also be done in different possible ways. Other quantitative measures for describing chiral discrimination are available in the literature.[28] We took the simple approach to start with the orientation at the lowest energy (optimum) of the corresponding pairs and subsequently followed by 2π rotation. Thus, the mapping shows that if one starts from the optimum geometries of the L−L and D−L pairs and rotates one molecule relative to the other, the L−L pairs will pass through relatively low-energy surfaces. However, it is obvious that other ways of mapping would not change the relative favorable nature of the L−L surface compared with D−L as shown in Figure 5. The discrimination depicted in Figure 5 also aims not to compare the regions where the pair of molecules are forced into regions of high steric repulsions and hence compare unphysical situations. We recognize that during the A−P rotatory motion, L−L and D−L have to pass through orientations other than that of the intermolecular mutual orientation which corresponds to the optimized geometry of the pair of molecules (while the individual molecules may remain in their optimized geometry). This passage is easier for the L−L pair rather than the D−L pair. In other words, during the A-to-P rotatory process, the L−L pair will pass through relatively low-energy regions compared with the D−L pair.

We also studied the discrimination of zwitterionic pairs of L−L and D−L alanine to understand if the effect of electrostatic interaction alters the observed discrimination. The energy profiles for L−L and D−L zwitterionic alanine pairs are shown in Figure 6. Similar to the neutral molecules, the energy profiles of L−L and D−L zwitterionic pairs are also dissimilar. The range of the variation in energy in the case of the zwitterionic pair is more than the same observed for the neutral pair due to the presence of a charge−charge interaction which is one of the strongest intermolecular interactions. Similar to the case of neutral pairs, the orientational space for the favorable L−L interaction is more selective than the corresponding space for the D−L pair in the case of zwitterionic molecules. However, unlike the neutral case, the asymmetric charge distribution in the optimized geometry of the neighboring molecules (starting geometry) breaks the symmetry of the energy profile of the D−L zwitterionic pair, which can be observed in the corresponding dissymmetric nature of the energy profile.

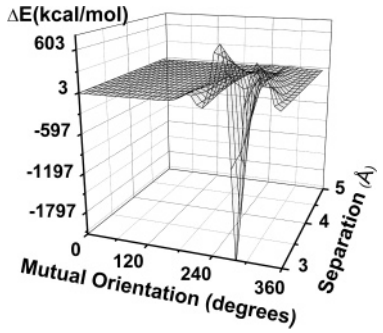

Figure 7. Chiral discrimination energy (ΔE_{LL-DL}) calculated from the ab initio (HF/6-311++G**) potential energy surface of pairs of zwitterionic L−L and D−L alanine molecules as shown in Figure 6 as a function of orientation and distance.

The plot of ΔE_{LL-DL} with variation in the $C^{\alpha}-C'-O'\cdots N$ dihedral angle at given distances is shown in the Figure 7 for zwitterionic alanine pairs. The largest discrimination is observed at the separation at the minimum energy (2.69 Å) and not at the orientation corresponding to the optimized geometry of the respective pairs similar to the situation in neutral alanine. Maximum homochiral discrimination is observed around 280° relative to the corresponding dihedral angle at optimized geometry. The hydrogen atom of the second amino group of D-alanine is in steric hindrance with the oxygen atom of the second carboxylic group of L-alanine at 280° relative orientation (the respective second group indicates those groups not involved in the $C^{\alpha}-C'-O'\cdots N$ dihedral angle rotation; see parts a and b of Figure 3, respectively), and the rise in energy due to short-range steric repulsion is largest at this orientation. This is due to the strong short-range overlap of atoms in the zwitterionic D−L pair. On the other hand, in the case of the L−L zwitterionic pair, the second carboxyl of the L-molecule and the second amine of the D-molecule are at close proximity at the 280° relative orientation. This gives rise to the short-range electrostatic attraction. Thus, the favorable electrostatic interaction is further contributing to the large homochirality of ΔE_{LL-DL} for the zwitterionic pair in addition to the short-range steric repulsion (which is the major source of discrimination for neutral molecules).

The energy profile for the interaction for a pair of glycine molecules is shown in Figure 8. The plot resembles the plot of pair energy of the D−L neutral alanine pair, reflecting the underlying achiral nature of glycine. This is in accordance with the recent calculation based on effective potential that achiral molecules have an interaction profile with achiral molecules that is symmetric.[6]

We calculated the BSSE by the counterpoise method at a few points where maximal chiral discrimination is observed for neutral and zwitterionic pairs. The aim is to note the extent of BSSE in the energy profile. The results are shown in Figure 9. It is seen that BSSE correction enhances the discrimination at the HF level. We also calculated ΔE_{LL-DL} using the MP2/6-

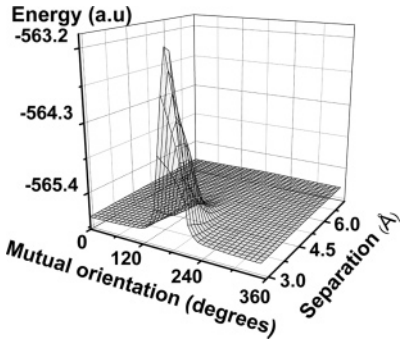

Figure 8. Ab initio (HF/6-311++G**) potential energy surface of a pair of zwitterionic glycine molecules as a function of orientation and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair.

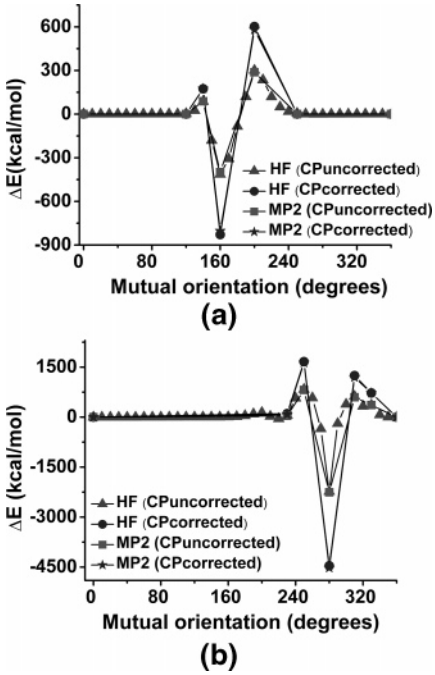

Figure 9. Comparison of the counterpoise-corrected result which is BSSE free (denoted by $CP_{Corrected}$) and uncorrected result (denoted by $CP_{Uncorrected}$) of the slice of the chiral discrimination energy (ΔE_{LL-DL}) plot as shown in Figures 5 and 7, respectively, for (a) neutral and (b) zwitterionic alanine molecules. The plots correspond to the distance at which the maximal homochirality and heterochirality are observed in the respective uncorrected energy surfaces (Figures 5 and 7, respectively). The line with triangles indicates the energy plot for the BSSE uncorrected profile using chiral discrimination energy ΔE_{LL-DL} values (Figures 5 and 7, respectively) at the HF/6-311++G**. The line with filled circles indicates the energy plot for the BSSE corrected profile of chiral discrimination energy ΔE_{LL-DL} values at the HF/6-311++G**. Similarly, the line with filled squares indicates the energy plot for the BSSE uncorrected profile using chiral discrimination energy ΔE_{LL-DL} values at the MP2/6-311++G**. The line with asterisks indicates the energy plot for the BSSE corrected profile of chiral discrimination energy ΔE_{LL-DL} values at the MP2/6-311++G**.

311++G** theory which is shown in the same plots and further corrected the BSSE using the same level of theory. The plots of HF level and MP2 level are closely similar relative to the observed range of discrimination. Hence, the observed discrimination in the present work is not significantly dependent on basis set or BSSE.

A comparison of selected structural parameters of the optimized structure of the neutral and zwitterionic L−L and D−L alanine molecules at the HF and the DFT levels of theory is made in Tables 6 and 7 of the Supporting Information. Also, a

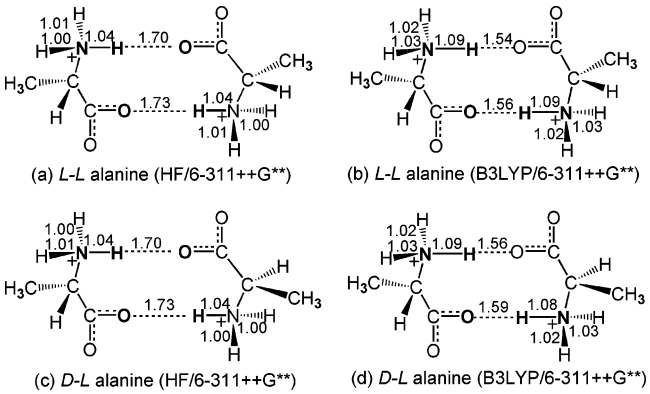

Figure 10. Schematic comparison of the geometrical parameters of the optimized zwitterionic alanine molecule (a) for the L−L pair using the ab initio (HF/6-311++G**) method, (b) for the L−L pair using DFT (B3LYP/6-311++G**), (c) for the D−L pair using the ab initio (HF/6-311++G**) method, and (d) for the D−L pair using DFT (B3LYP/6-311++G**).

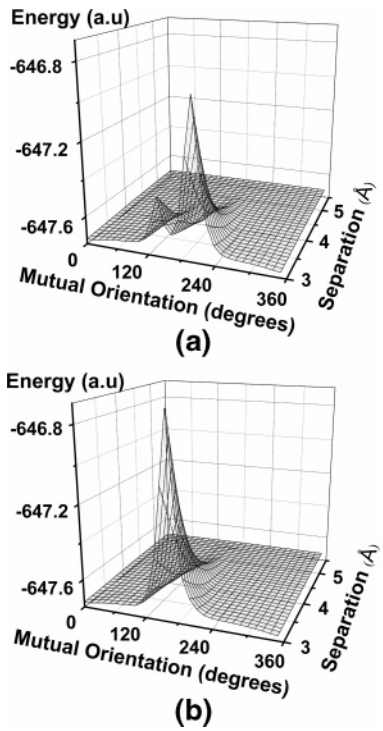

Figure 11. (a) DFT (B3LYP/6-311++G**) potential energy surface of a pair of neutral L−L alanine molecules as a function of orientation (as shown in Figure 2a) and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair, and (b) the DFT (B3LYP/6-311++G**) potential energy surface of a pair of neutral D−L alanine molecules as a function of orientation (as shown in Figure 2b) and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair.

comparison of the geometry of the zwitterionic alanine molecules (L−L and D−L) optimized at the HF and B3LYP levels of theory is made in Figure 10. The energy profiles of the L−L and D−L pairs of neutral alanine calculated using the B3LYP/6-311++G** theory are shown in Figure 11 as a function of distance and orientation with variation in the $C^{\alpha}-C'-O'\cdots N$ dihedral angle. The plot of the L−L pair is dissymmetric revealing the underlying chirality of the molecules. On the contrary, the plot for the D−L pair is symmetric around 180° orientation, which reveals the racemic state of the neutral pair. Both plots show gradually diminishing interaction when the molecules are far separated. The features calculated at the DFT

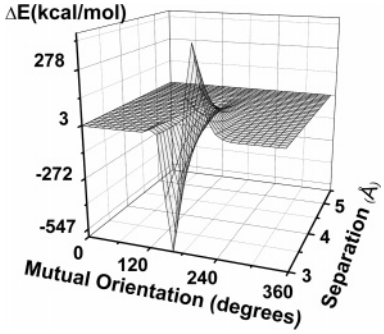

Figure 12. Chiral discrimination energy (ΔE_{LL-DL}) calculated from the DFT (B3LYP/6-311++G**) potential energy surface of pairs of neutral L−L and D−L alanine molecules as shown in Figure 11 as a function of orientation and distance.

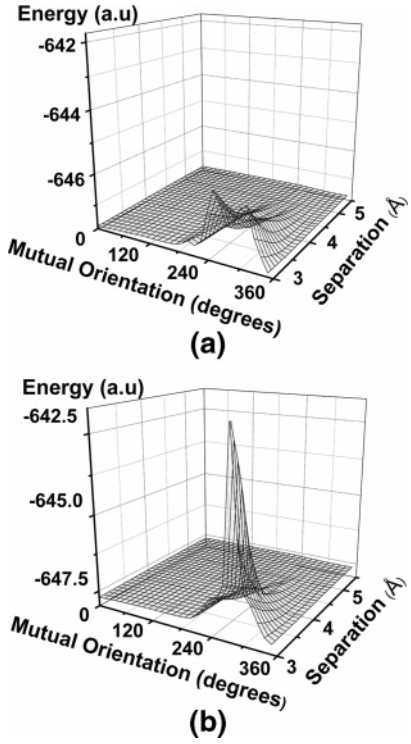

Figure 13. (a) DFT (B3LYP/6-311++G**) potential energy surface of a pair of zwitterionic L−L alanine molecules as a function of orientation (as shown in Figure 3a) and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair, and (b) the DFT (B3LYP/6-311++G**) potential energy surface of a pair of zwitterionic D−L alanine molecules as a function of orientation (as shown in Figure 3b) and distance (see section II for details) with rigid geometry starting from the optimized structure of the pair.

level of theory are similar to those calculated at the HF level of theory. The plot of ΔE_{LL-DL} with variation in the $C^{\alpha}-C'-O'\cdots N$ dihedral angle calculated using the B3LYP/6-311++G** theory is shown in the Figure 12 for neutral alanine pairs. The plot indicates that L−L interaction is relatively more favorable in the range of orientation investigated and the feature is similar to that observed at the HF level. The energy profiles for the L−L and D−L zwitterionic alanine pairs, calculated using B3LYP/6-311++G** theory, are shown in Figure 13. The features of these plots are similar to those observed at the HF level of calculation. The plot of ΔE_{LL-DL} with variation in the $C^{\alpha}-C'-O'\cdots N$ dihedral angle at given distances is shown in the Figure 14 for zwitterionic alanine pairs, and the plot shows similar chiral discrimination as observed in the HF level of calculation. A comparison of the results obtained at the HF level

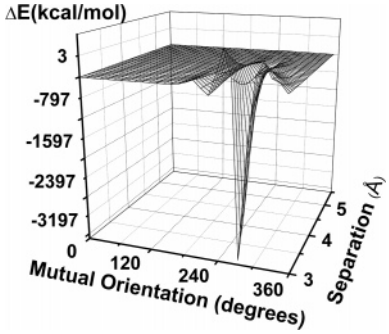

Figure 14. Chiral discrimination energy (ΔE_{LL-DL}) calculated from the DFT (B3LYP/6-311++G**) potential energy surface of pairs of zwitterionic L−L and D−L alanine molecules as shown in Figure 13 as a function of orientation and distance.

and DFT level of theory for both neutral and zwitterionic L−L as well as D−L pairs indicates that the conclusions made in the present work are independent of the two theoretical methods employed.

The observed orientation dependence of the chiral discrimination is relevant to the process of peptide biosynthesis where the proximity effect is known to be important. It is obvious that there would be little or no energetic advantage of L−L synthesis over D−L synthesis provided the interaction energy profile for the rotational motion of the A-to-P site is independent of the mutual orientation of the concerned chiral species. The chiral discrimination observed due to steric interaction could influence the preferred L-amino acid incorporation. It is interesting to note that the maximal value of $\Delta E_{LL-DL}^{Homochiral}$ (observed homochiral preference) is larger than the maximal value of $\Delta E_{LL-DL}^{Heterochiral}$ in the same plot (observed heterochiral preference) for both the neutral and zwitterioic pairs of alanine using both the HF and the DFT levels of theoretical calculation. To the best of our knowledge, this is the first observation of the orientation-dependent homochiral discrimination in the case of alanine without the use of parameters in theoretical calculation. Note that the orientation dependence is predicted in recent theories based on effective pair potential theories and is not studied in the extensive simulation of Andelman and coworkers.[1−6,9,10] This work confirms our previous conclusion based on the pair potential theory that the chiral discrimination is dependent on mutual orientation of the molecular pair concerned. Two major reasons for preferred homochirality are as follows: First is the various short-range steric overlaps in the case of the D−L pair, which does not occur for the L−L pair. Second, the short-range electrostatic interaction further augments the homochirality in the case of the zwitterionic pair.

However, a limitation of the present study is that the present calculation is based on the alanine molecule with neutral and zwitterionic states, which is different from the structural and ionization states of the amino acid segments at the A- and P-sites. Hence, at present we can only conclude about the preferred homochirality of the isolated molecules. It is also to be noted that a new stereocenter is generated during the peptide synthesis with the tetrahedral intermediate (Figure 1). Hence, the intermediate formed by the L−L pair and D−L pairs have a diastereomeric relationship and could further contribute to the observed discrimination. Another necessary extension of the present work is to incorporate the effect of neighboring groups other than the amino acid segments themselves in the present scheme of calculation of the energy profile. It is expected that the effect of the chirality of the surrounding groups would further enhance discrimination as suggested by effective pair

potential theories.[1−6] A more detailed study considering the foregoing points is underway.

It is recently argued that the addition of an enantiomer with different ("wrong") chirality to a growing polymer might bring polymerization to a halt during the development of RNA from an achiral pre-RNA and can contribute to the plausible mechanisms which led to todays homochiral world.[29] The chirality of the incorporated amino acid into a growing polypeptide chain also might be imporant and can contribute to the amplification of the chirality. In such a case, the orientation dependence of the intermolecular interaction during incorporation of amino acids into a growing polypeptide chain could play a role as studied in the present work.

Summarily, we studied chiral discrimination in the orientation dependence of the intermolecular interaction of a pair of alanine molecules in their neutral and zwitterionic states. The calculation is carried out using ab initio theory (HF/6-311++G**) for both the homochiral pair (L−L) and heterochiral pair (D−L). Starting from the optimized structure, the energy surface is studied with rigid geometry by varying the distance and orientation between molecules. The study reveals clear discrimination and homochiral preference for the first time without use of parameters. It shows that the energy surface of the homochiral pair is more favorable in nature than the same of the heterochiral pair. Nonmonotonic distance and orientation dependence is observed. The discrimination is due to short-range steric repulsion, which is more in the case of the heterochiral pair than the same in the case of the homochiral pair. The present study opens up one possible way of D-amino acid exclusion. This is due to more steric hindrance between D- and L-amino acids themselves than the L−L pair and concomitant homochiral preference. The electrostatic interaction in the homochiral pair further augments the homochirality in the case of zwitterionic pair. The BSSE corrected result shows enhanced discrimination. The use of a higher-level theory (MP2) and further BSSE calculation at the same level do not change the conclusions made in the HF level of theory. The major conclusions remain unaltered when the calculations of the potential energy surfaces for neutral and zwitterionic pairs are performed using the DFT (B3LYP/6-311++G**) level of theory. It is known that the proximity and orientation play a significant role in peptide biosynthesis. The orientation dependence observed has significance in the chiral discrimination and chiral recognition processes in general as well as in the process of peptide synthesis at the peptidyl transferase center where the interaction between the amino terminal and the peptidyl terminal has orientation dependence.

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Supporting Information Available: Table 1: The Cartesian coordinates of the atoms of the pair of neutral L−L and D−L alanine molecules at the HF level of theory. Table 2: The Cartesian coordinates of the atoms of the pair of zwitterionic L−L and D−L alanine molecules at the HF level of theory. Table 3: The Cartesian coordinates of the atoms of the pair of neutral L−L and D−L alanine molecules at the DFT level of theory. Table 4: The Cartesian coordinates of the atoms of the pair of zwitterionic L−L and D−L alanine molecules at the DFT level of theory. Table 5: The conformational energy of L-alanine, D-alanine, a pair of L−L alanines, and a pair of D−L alanine molecules in their neutral and zwitterionic state at their respective optimized geometries. Superscript "N" indicates neutral species and "Z" indicates zwitterionic species. Table 6: The comparison of selected structural parameters of the optimized structure of the neutral L−L and D−L alanine molecules at the HF and the DFT levels of theory. Table 7: The comparison of selected structural parameters of the optimized structure of the zwitterionic L−L and D−L alanine molecules at the HF and the DFT levels of theory. This material is available free of charge via the Internet at http://pubs.acs.org.

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