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Theoretical Comparison between Three-Point and Two-Point Binding Modes for Chiral Discrimination upon the N-Terminal Sequence of 3_{10}-Helix

Yoshihito INAI,† Naoki OUSAKA, and Yoichi MIWA

Department of Environmental Technology and Urban Planning, Shikumi College, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan

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ABSTRACT: Complex structure and its energy were theoretically predicted between the N-terminal segment of right-handed 3_{10}-helical peptide (**1**) and chiral acid based on various amino acids. Two categories of the chiral acids have been chosen. One is *N*-carbonyl-blocked amino acid for the three-point coordination to the N-terminal sequence of peptide **1**. The other acid for the two-point coordination contains no extra carbonyl groups. Energy minimization from the corresponding initial models was performed by semiempirical molecular orbital calculation. In each amino acid species, the three-point coordination, compared with the two-point type, tends to generate larger difference in energies of D-/L-complexes, which are more stable for L-species bound to right-handed helix. In the three-point binding, *N*-carbonyl-blocked L-amino acid is prone to adopt negative ϕ values. Density functional method was also applied to smaller analogs, providing similar tendency in complex structure and energy difference. The predictions obtained here are fully consistent with our previous findings [Y. Inai *et al.*, *J. Am. Chem. Soc.*, **125**, 8151–8162 (2003)], in which preferential induction of right-handed helix in peptide **1** occurs with *N*-carbonyl-protected L-amino acid, but inefficiently with simple carboxylic acid. The energetic advantage for the three-point binding implies the function of 3_{10}-helical N-terminus to discriminate the chirality of *N*-carbonyl-blocked peptide acid molecule.
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KEY WORDS Chiral Discrimination / 3_{10}-Helix / N-Terminus / Three-point Interaction / Molecular Orbital Calculation / Chirality of Amino Acid / Helix Sense /

Peptide and protein helices usually accompany free amide groups at both termini due to periodic intramolecular hydrogen bonds between remote residues along their single chain.[1] The interactive nature of the terminal motifs has often been noticed from the viewpoint of biological structures, functionalities, and implications.[1] We[2] recently discovered screw-sense induction in 3_{10}-helical backbone[3] through complex formation between its N-terminal segment and chiral additive. This phenomenon, coined as the *noncovalent chiral domino effect* (NCDE),[2a,b,e] also implies that N-terminal 3_{10}-helical sequence functions as chiral discriminator by means of the three-point binding, in which the N-terminal amino group and two free NH's of second and third residues cooperatively capture an external chiral molecule.[2a,b] The occurrence of the three-point interactions were experimentally or theoretically shown for limited chiral species.[2a,b,f] However, the energetic advantage of the three-point interactions is not theoretically proven in chiral discrimination upon the 3_{10}-helical N-terminus, whereas the three-point coordination has been widely accepted for other chiral recognition systems.[4,5]

In order to clarify the essential difference between the three-point and two-point interactions,[6] we here have carried out systematic, theoretical screening of various chiral acids for chiral discrimination of nonapeptide (**1**), H-β-Ala-(Δ^{Z}Phe-Aib)$_4$-OCH$_3$[2a] (**1**: β-Ala = β-alanine; Δ^{Z}Phe = *Z*-didehydrophenylalanine; Aib = α-aminoisobutyric acid), that is assumed to adopt essentially a right-handed 3_{10}-helix: for the details, see the experimental section.

Two categories of chiral additives have been chosen in the presence and absence of extra hydrogen-bond accepting groups. One is N-blocked amino acid (**2**–**5**) having a urethane or amide group, while the other acid (**6**–**9**) contains no extra carbonyl groups. Stable structure and energy value for each complex were predicted from semiempirical molecular orbital (MO) calculation (the AM1 method).[7] Leucine (Leu), Ala, valine (Val), phenylalanine (Phe), and proline (Pro) were used as the parent chiral compounds. Pro is similarly defined by functionality of Chart 1. **9**(Ala and Pro) and **8**(Pro) are missing due to their chemical structures, while **7**(Pro) is N-monomethyl Pro.

Our present purpose is not to comprehensively find out the most stable form for complexation only by theoretical basis, but rather to explain the previous experimental tendency[2a] to suggest significant chiral discrimination of 3_{10}-helical N-terminus. In particular,

†To whom correspondence should be addressed (Tel: +81-52-735-5271, Fax: +81-52-735-5247, E-mail: inai@mse.nitech.ac.jp).

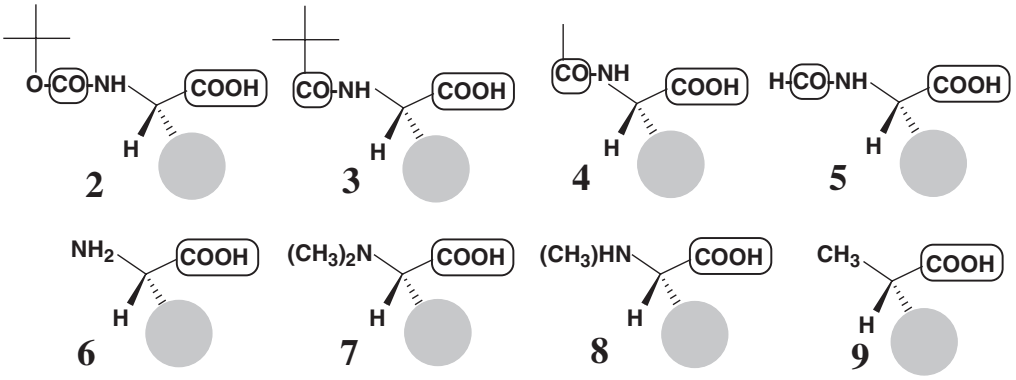

Chart 1. Summary of chiral species based on L-amino acid for complexation: functional groups for coordination to the N-terminal 3_{10}-helix are highlighted with enclosures.

we here attempt to elucidate theoretical answer as to why chiral acids [*e.g.*, Boc-amino acid (Boc = *t*-butoxycarbonyl)] capable of the three-point binding to the N-terminal segment induce preferentially a one-handed helix of peptide **1**, whereas such efficient induction in helix sense does not occur with simple carboxylic acids suggesting the two-point binding.[2a] Correspondingly, complex structure has been energy-optimized from each of initial conformers built on the basis of the concept described in ref 2a. Simulated complexes have been energetically compared in **2**–**9** species based on various amino acids to figure out essential difference between the three-point and two-point binding modes in chiral recognition leading to helix-sense induction.

Computation based on density functional theory (DFT)[8,9] was also carried out for some complexes of a shorter helical analog. The present theoretical results reveal that the three-point binding mode has energetic advantage of effective chiral discrimination over the two-point binding.

EXPERIMENTAL

Estimation of Theoretical Complex by Semiempirical MO Computation

Peptide **1** was previously shown to take 3_{10}-helical conformation where the Δ^ZPhe(4) to Aib(9) NHs undergo intramolecular hydrogen bonds between (*i*) and ($i + 3$) residues.[2a,3] Such helical structure should be essentially maintained in complexation with Boc-amino acid, because the above six NH resonances were insensitive to addition of Boc-amino acid.[2a] Achiral sequence of peptide **1** originally yields completely mirror symmetry in the right-handed and left-handed helical forms. Thus, the complex of chiral additive/peptide **1** ought to keep enantiomeric relation for L/right-handed helix and D/left-handed helix (or for D/right-handed helix and L/left-handed helix). Although the choice of helix sense in the initial modeling is not significant issue, we here have chosen right-handed helix common to natural protein segments.[3] Thus, complexes of L/right-handed helix and D/right-handed helix are simulated for each additive and compared in L-/D-isomers of each amino acid-based species as follows.

Theoretical complex structures as well as their energies were obtained from the AM1 method in MOPAC97.[7] Similar computation was already performed for combination of right-handed 3_{10}-helical peptide **1** and Boc-amino acid (Leu or Pro).[2a] The molecular docking manner assumed for energy minimization is based on the concept of the following three-point coordination.[2a] Here complexation of Boc-amino acid and peptide **1** in chloroform is characterized by the three-point binding upon the N-terminal 3_{10}-helical segment: *i.e.*, one ionic interaction ($-COO_2^-$ NH_3^+-) and two hydrogen bonds [carboxylate O atom versus Aib(3) NH; urethane carbonyl O atom versus Δ^ZPhe(2) NH].[2a] Acid-base interaction often generates effective induction of chirality in other unique molecular systems.[10]

In the present study, various types of complexes were estimated basically according to the following procedures. First, complex structure of peptide **1** with Boc-amino acid was computed (or re-computed for Leu and Pro). As mentioned above, complex structures of right-handed 3_{10}-helical peptide **1** with Boc-(L/D)-Leu-OH or Boc-(L/D)-Pro-OH were obtained through similar energy computation.[2a] Theses complex structures,[2a] supported by the three-point coordination, were basically used here to recalculate complex of Boc-(L/D)-Leu-OH or Boc-(L/D)-Pro-OH, or to build each initial complex of the remaining Boc-amino acids. For the latter case, the isobutyl group of Boc-Leu-OH was changed to methyl (Ala), benzyl (Phe), or isopropyl (Val) group. Some side-chain orientations of Boc-amino acid [(χ^1, χ^2) of Leu and Phe, and χ^1 for Val][11,12] were taken into account, because they often influence complex structures optimized and

their energy values. It should be noted that these modelings are restricted to the three-point coordination proposed previously.[2a] We did not attempt comprehensive searching of initial complex structures including another type of three-point coordination.

AM1-based energy minimization[7] was carried out for each complex. During the minimization process, three N–H bond lengths of the ammonium head were kept at 1.025 Å.[2b] A keyword of 'MMOK' for correction of rotational barrier around peptide bond[7a–d] was applied here likewise in our previous studies.[2a,b] The structure optimization was carried out by using 'EF'-method together with 'GEO-OK' and 'PRECISE'.[7] 'SCFCRT=1.D-11' was also specified for criterion of the SCF solution.[7a–d] Three additional keyword sets were also specified to each geometry, that is 'GNORM=0.01 CYCLES=50000 LET DDMIN=0.0', 'GNORM=0.01 CYCLES=50000', or 'CYCLES=50000'.[7] Process and termination for each optimization followed the program's judgment. Among complexes converged from initial conformers generated in the preceding way or the minimization conditions mentioned above, we picked up, for each Boc-(D or L)-amino acid (**2**), one stable complex with its energy value (defined as "heat of formation"[7a–d] in kcal mol^{-1}).

For the other species (**3**–**9**), each initial complex structure was basically produced from partial substitution in the corresponding Boc-amino acid (**2**)-complex picked up above. For instance, the $(CH_3)_3CO$- moiety in the **2**-complex was changed to CH_3- moiety in the corresponding **4**-complex, while being changed to H- in the corresponding **6**-complex. This procedure allows these initial structures to be specified to the three-point coordination for **3**–**5** acids having one additional carbonyl group similar to **2**, and to be specified to the two-point coordination for **6**–**9** lacking extra carbonyl groups. The two-point coordination in **6**–**9** is based on one ionic interaction ($-COO_2^-$ NH_3^+-) and one hydrogen bond [carboxylate O atom versus Aib(3) NH]. This modeling should be supported by the experimental fact that simple carboxylic acid is preferentially accessible to the Aib(3) NH group of peptide **1**.[2a] Similarly to the case of **2**-complex, energy minimization in **3**–**9**-complexes was carried out for each initial structure to yield the respective complex and its energy value. Re-optimization from conformer (**2**–**9**) selected through the above procedure was carried out to check the validity of the energy-minimization process.

According to the modeling procedure, H^α proton of L-isomers **6**–**9** is roughly directed to the looping shape of H-β-Ala-Δ^ZPhe(2)-Aib(3)-, while the D-isomers' H^α takes the opposite direction. However, rotation around each C^α-atom of **6**–**9** should not be prohibited in geometry of the two-point coordination. Thus, each complex (**6**–**9**) picked up through energy minimization of initial conformers made in the first concept was rotated around the C^α atom by 180°: that is, σ (torsion angle of O–C–C^α–H^α) was changed to ($\sigma - 180°$) or ($\sigma + 180°$). Complex modified in this way was also considered for another initial conformer.

As mentioned before, our calculation is not intended to search the global-minimum point for complexation. Meanwhile, Δ^ZPhe side-chain orientations (χ^2-rotation) were considered in complex structure, since they tend to alter complex energies to some extent. In the AM1-level calculation,[7] these energy values essentially lower in the geometry re-optimized from complexes modified with $\chi^2 = 40°$[13] [Δ^ZPhe(2,6,8) or Δ^ZPhe(2,4,6,8)], in which the Δ^ZPhe phenyl faces with $\chi^2(\Delta^Z\text{Phe}) = 40°$ take a direction roughly perpendicular to the helix axis (type I orientation). (Here the phenyl orientation of Δ^ZPhe(4) around $\chi^2 = 40°$ is sterically unstable due to the proximity to the N-ammonium terminus.) On the other hand, our previous studies[2a,b] reported theoretical complex structures with orientation of phenyl faces essentially-parallel to the helix axis (type II orientation). A similar orientation was found in crystal of analogous 3_{10}-helical nonapeptide.[14] Based on the experimental finding, we here adopt mainly complex structures in type II orientation, while the corresponding complexes with type I orientation are also presented for comparison. Other examples of theoretical studies on conformational nature of dehydroresidues were reported in refs 13–15.

Procedure for DFT-Computation

Simulation with the B3LYP/6-31G(d,p) method in Gaussian 03[8,9] was also carried out for complex of shorter analogous H-β-Ala-Δ^ZPhe-Aib-Δ^ZPhe-$NHCH_3$ (**1′**) and L-/D-**4** or **6**(Ala). To ensure terminal ionic interaction during the minimization course, three bond lengths of ammonium N–H were fixed to 1.026 Å, which was obtained from H_2^+-β-Ala-$NHCH_3$ energy-minimized with the DFT-computation. The AM1[7]-optimized complexes of L-/D-**4**(Ala) or L-/D-**6**(Ala) with **1** based on type II orientation were used for the respective initial modeling for the density functional method. Each optimization process and termination followed the program's judgment.

Molecular graphics of complex structures for the present paper were drawn mainly with *Arguslab*.[16]

RESULTS AND DISCUSSION

Theoretical Complex Structure

Complex structures for the Leu species obtained by the semiempirical MO (AM1) method[7] are given in Figure 1. When chiral molecule (**2**–**5**) contains a ure-

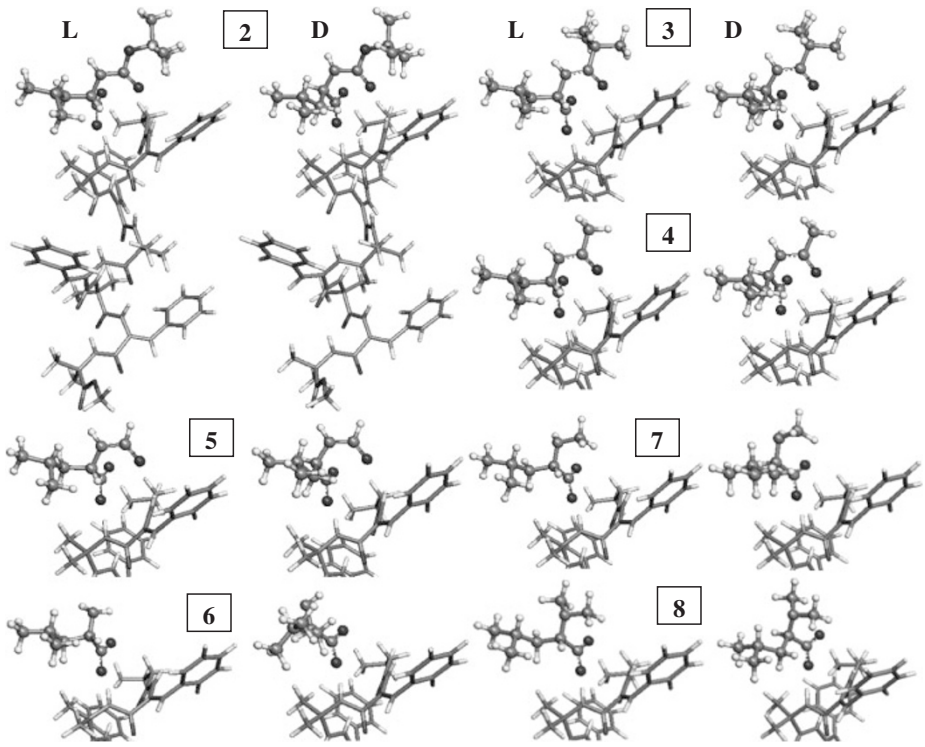

Figure 1. Complex structures of peptide **1** with Leu-based species (**2**–**8**), obtained by the AM1 method.[7] The L-isomer and D-isomer are indicated in left- and right-sides of each. In **3**–**8**, only the N-terminal moieties of peptide **1** are drawn for simplification.

thane or amide group, the three-point interactions in its initial modeling are assumed as described in the experimental section. These binding manners are experimentally and theoretically proposed for Boc-Pro-OH or Boc-Leu-OH.[2a] Structure-optimized complexes essentially retain the three-point interactions on the 3_{10}-helical N-terminus. A carboxylate group of the external chirality is close to the ammonium head (H_2^+-β-Ala-), while either oxygen atom of the carboxylate group is hydrogen-bonded to the Aib(3) NH. Thirdly, the remaining urethane or amide carbonyl group forms a hydrogen bond with the Δ^ZPhe(2) NH. On the other hand, species (**6**–**9**) without extra carbonyl groups essentially retain the two-point interactions assumed for the initial conformations, wherein the carboxylate group binds the ammonium head and Aib(3) NH.

The corresponding D-Leu isomer also undergoes essentially the three-point interactions in **2**–**5**, and the two-point interactions in **6**–**9**. Similar interaction manner was drawn in the other amino acid species with and without extra carbonyl groups. Therefore, the *N*-carbonyl-blocked amino acid, defined as "peptide acid", possesses a clear propensity to undergo the three-point binding to the N-terminal sequence of a 3_{10}-helix.

Energy Difference in D-/L-Complexation

The energy difference between complexes of D-/L-isomers (**2**–**9**) with right-handed 3_{10}-helix (**1**) [ΔE_{D-L} (kcal mol^{-1}) = $E_{complex}$(D) − $E_{complex}$(L)] is graphically summarized in Figure 2 for more quantitative discussion. Here the Leu species without extra carbonyl groups (**6**–**9**) yields a relatively small ΔE_{D-L} value in its complex. In contrast, the *N*-carbonyl-blocked Leu-based species (**2**–**5**) afford more prominent energy bias (above *ca.* 1.5 kcal mol^{-1}).[17] Consequently, changes in interaction mode from the two point to the three point generate a remarkable energy bias in chiral complexation. This also demonstrates that the three-point coordination complementing the three free sites of 3_{10}-helical N-terminus play a significant role for chiral discrimination.[2a] Similar tendency is seen for the Ala, Phe, and Pro species: a relatively large ΔE_{D-L} value (> *ca.* 1.5) for **2**–**5** and a small ΔE_{D-L} value (< *ca.* 1.0) for **6**–**9**. Similarity in ΔE_{D-L} values of these four species implies that the steric effect of β-mono-substituents in the Leu and Phe residues is substantially insensitive to the efficiency of chiral discrimination. Meanwhile, the ΔE_{D-L} values in the Val species are somewhat different from those of the preceding residues: *i.e.*, a larger ΔE_{D-L} value is commonly provided for their species **2**–**5** (ΔE_{D-L} > *ca.* 4). The pronounced energy bias might be relevant to steric restriction around the chiral center (C^α) attached to the disubstituted-C^β atom (Val). It is not straightforward to interpret the precise correlation between ΔE_{D-L} value and the degree of experimentally-

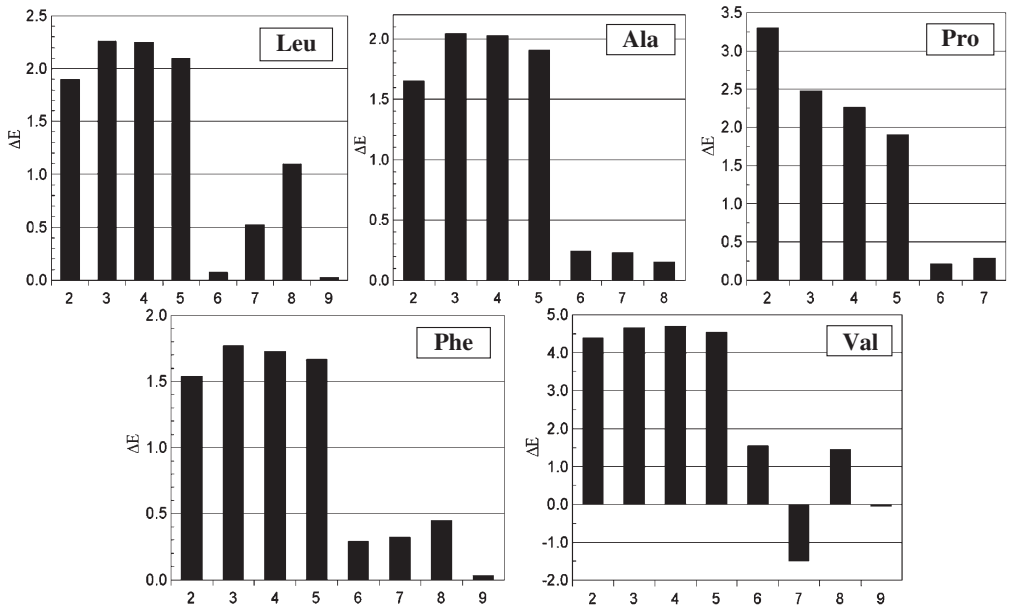

Figure 2. Energy difference (ΔE_{D-L}, kcal mol^{-1}) in complexes of D- and L-amino-acid-based species versus right-handed helical peptide **1**.

induced bias to a one-handed helix.[2a] For instance, Boc-Val-OH showing such large ΔE_{D-L} value does not always induce a larger CD amplitude of peptide **1** than the other Boc-amino acids do.[2a]

However, common tendency in ΔE_{D-L} values of the five kinds of amino acid-based species strongly supports that the three-point binding upon the 3_{10}-helical N-terminus takes advantage of energy bias for effective chiral discrimination over the two-point binding. This conclusion from the theoretical aspect agrees well with the experimental observation that chirality transfer to peptide **1** occurs effectively with Boc-amino acid or propyl-CO-L-Leu-OH, but inefficiently or not with a simple chiral carboxylic acid.[2a]

Chiral acids **2**–**5**, independent of the amino-acid type and N-terminal protecting group, produce positive values in ΔE_{D-L}, suggesting that these L-species are preferentially complexed with right-handed helix. While this tendency was partly pointed out,[2a] a wide variety of L-species capable of the three-point coordination is demonstrated to potentially induce right-handed screw sense in the 3_{10}-helix.

The origin of energy difference in the three-point complexation (**2**–**5**) has been focused on.[18] After peptide **1** and chiral additive were separated from the original complex, energy values of the respective ionic fragments, E_1 and E_{add}, were calculated. Then, energy difference in D-/L-complexes based on E_1 and E_{add} was estimated as ΔE_1 and ΔE_{add}, respectively, which are summarized in Figure 3 together with the corresponding ΔE_{D-L} values. Figure 3 also shows these energy differences obtained from complexes of peptide **1** adopting essentially different side-chain orientations in Δ^ZPhe(2,6,8): for the detail, see the experimental section. A general tendency in these values is similar to each of the two side-chain orientation (type II and type I) manners in Δ^ZPhe(2,6,8), which should be less influential in complexation.

On the whole, complexes of **2**–**5**, except for the Pro species, indicate marked positive ΔE_{add} values, whereas the ΔE_1 values are less significant in comparison to the corresponding ΔE_{D-L}. Thus the different stability in complexation (ΔE_{D-L}) might be mainly ascribed to conformational energy of chiral additive (ΔE_{add}) that undergoes the three-point coordination to the 3_{10}-helical N-terminus, implying that the L-additive (**2**–**5**) geometry preferentially fits the N-terminal sequence of right-handed helix.

Conformation of each D-/L-amino acid species (**2**–**5**) in the corresponding complex, except for the D-Pro species, tends to adopt negative values for its main-chain torsion angle (ϕ). Here average ϕ values of **2**–**5** (Leu, Ala, Phe, and Val) are -65° (L) and -57° (D) for type II orientation (left side of Figure 3), and -70° (L) and -60° (D) for type I orientation (right side of Figure 3). Average ϕ's of **2**–**5**(Pro) are -49° (L) and $+56^\circ$ (D) for type II, and -51° (L) and $+69^\circ$ (D) for type I. This suggests that such negative ϕ value in these amino-acid species is a key conformation for the three-point binding to the N-terminus of right-handed 3_{10}-helix. Judging from general tendency that most of natural L-amino acid residues take negative ϕ value as seen in right-handed helices,[3,11a,19] it might be reasonable that the L-amino acid-based species enables more favorable fitting for the complexation. To check the speculation, the ϕ-dependence on energy

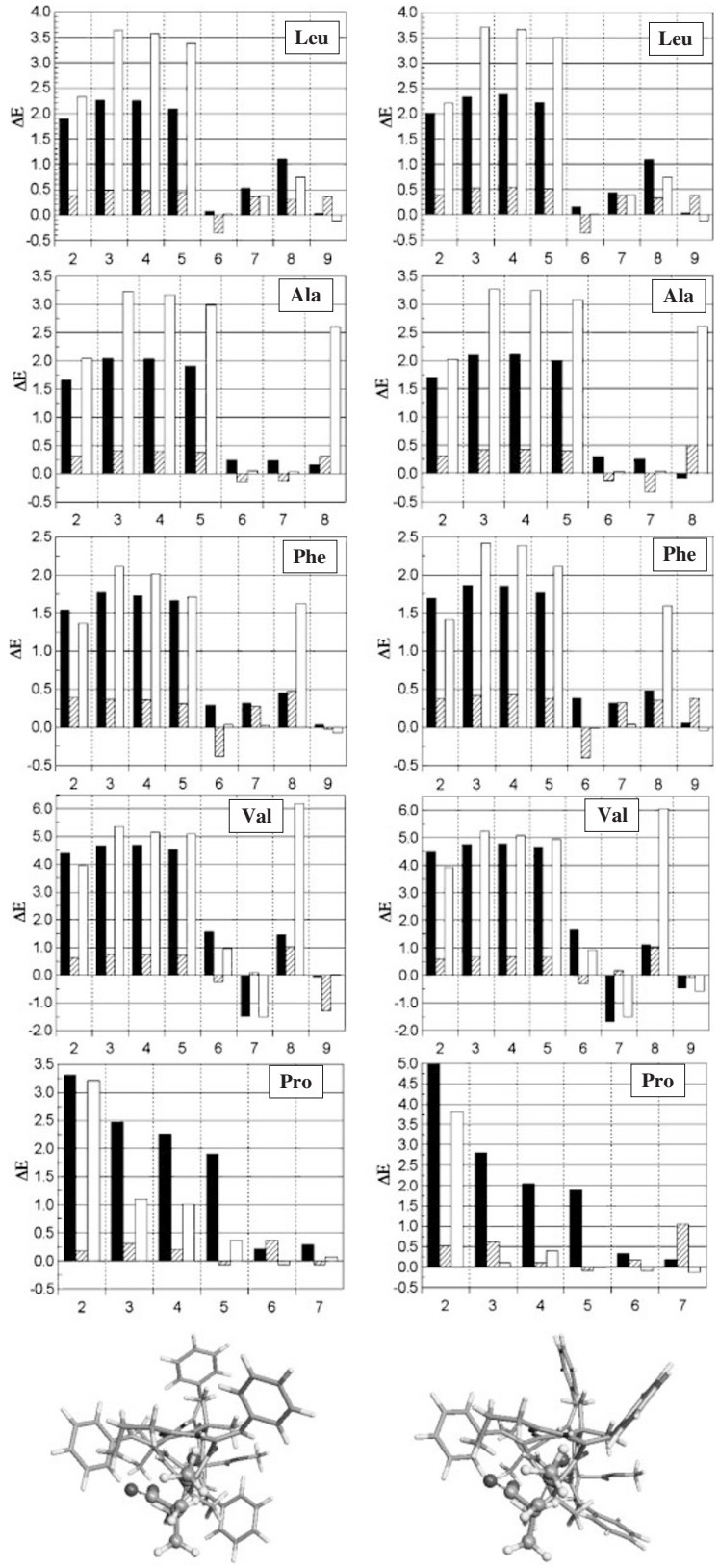

Figure 3. Energy differences in complexes with D- and L-additives (ΔE_{D-L}, kcal mol^{-1}): drawn with black bars according to Figure 2. Peptide **1** and chiral additive in each complex are virtually separated as ionic fragments to estimate the corresponding ΔE_1 and ΔE_{add} values, which are drawn with slashed and open bars, respectively. Left-side figures (type II orientation) correspond to Figures 1 and 2. Right-side figures (type I orientation) are based on peptide **1** with the phenyl orientations of Δ^ZPhe(2,6,8) that essentially differ from those shown in Figure 1 (see the text). Typical phenyl orientations of peptide **1** with L-**4**(Ala) are depicted in the respective bottom.

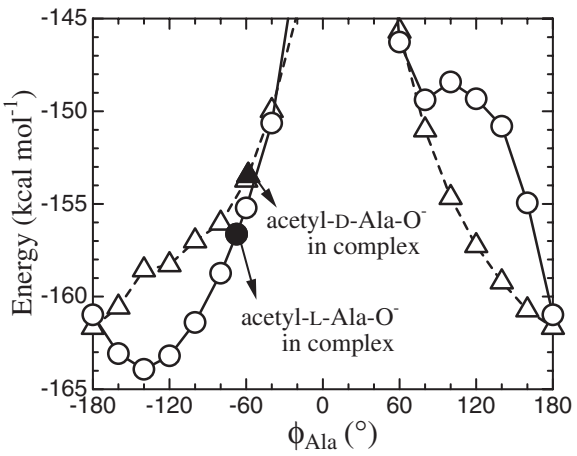

Figure 4. Theoretical ϕ(Ala)-energy correlation in acetyl-Ala-O^- with L (circle/solid line) and D (triangle/broken line) configurations. Energy ("heat of formation") was estimated from single-point SCF calculation in the AM1 method.[7a–d] The original structures were extracted from the corresponding complexes of **1** versus **4**(Ala). Their ϕ(Ala) and energy values are indicated by filled points. ϕ(Ala) in each original structure was changed by a step of 20° in −180° to +180° to generate the respective conformer to compute its energy. The same value is given at $\phi(\text{Ala}) = -180°$ and +180° due to the geometric equivalence.

value was estimated for acetyl-L-Ala-O^- or acetyl-D-Ala-O^- extracted from complexes of peptide **1** with **4**(Ala). The ϕ-energy profiles are displayed in Figure 4. They do not produce mirror symmetry between the D-/L-isomers, because the two original conformations are not equivalent due to the asymmetric binding to right-handed helix.

In the L-isomer, negative ϕ value yields lower energy value than the corresponding positive ϕ, whereas the D-isomer produces rough symmetry in ϕ and $(-\phi)$. On the whole, combination of the L-isomer and negative ϕ value should take energetic advantage, leading to preferential binding to right-handed helix. Thus, negative ϕ value preferred for most of L-amino acid residues, while generating right-handed sense in helix-forming sequences,[3,11a,19] might also be relevant to the preferential induction of right-handed helix through the noncovalent chiral interaction.

In the Pro-based species, ΔE_{add} is relatively large for **2**, but less significant for **5** in type II orientation and **3**–**5** in type I orientation. In contrast, the complexes of **2**–**5**(Pro) yield marked energy bias in ΔE_{D-L}. Thus, such marked ΔE_{D-L} value with less significant ΔE_{add} and ΔE_1 might originate from docking of the additive and peptide helix.

Complexes of **6**–**9** show less remarkable ΔE_1 in comparison to the corresponding ΔE_{D-L}, likewise in complexes of **2**–**5**. ΔE_{add} for **6**, **7**, and **9** is also less significant. Possibly, these species in the two-point coordination are suggested not to be restricted into unfavorable conformations. In contrast, complexes of **8** in Ala, Phe, and Val yield prominent ΔE_{add} values. The origin can not be clearly explained for now. On the other hand, the corresponding ΔE_{D-L} values are relatively small. Obviously, the marked energy bias originating in the fragment **8** (ΔE_{add}) does not reflect the ΔE_{D-L} in the additive-peptide complex, unlike the three-point binding case in **2**–**5**. This implies that the energy bias (ΔE_{D-L}) in complexes supported by the three-point coordination is more sensitive to energy bias originating in chiral additive's conformer as well as in docking process of the additive and helix.

DFT-Computation for Theoretical Complex

The preceding conclusions as well as our previous findings[2a,b] were derived from the semiempirical MO method, of which the AM1 parameterization[7] might affect these theoretical predictions. On the other hand, advanced simulation with *ab initio* or density functional levels, though significant, will need high cost and long term for our present molecular sizes. Correspondingly, peptide **1** was downsized to H-β-Ala-Δ^ZPhe-Aib-Δ^ZPhe-$NHCH_3$ (**1′**) to proceed to energy minimization of the complex of **1′**–**4** (Ala: acetyl-Ala-OH) or **1′**–**6** (Ala: H-Ala-OH) by means of the B3LYP/6-31G(d,p) level in Gaussian 03.[8,9] As described in the experimental section, the preceding AM1[7]-converged complexes (type II orientation) characterized by the three-point binding were basically used for each initial modeling.

Converged structures of peptide **1′** with L-**4**(Ala) or D-**4**(Ala) are displayed in Figure 5, and their structural parameters are listed in Table I. The three-point binding to both **4**-enantiomers is maintained upon the N-terminal sequence of peptide **1′** that essentially forms 3_{10}-helix. The two intermolecular hydrogen bonds appear to take more preferential forms,[6a] compared with those in the AM1[7]-derived structures (Table I). Complex of **1′**–L-**4**(Ala) is more stable by $\Delta E_{D-L} = ca.$ 2.4 kcal mol^{-1} than that of **1′**–D-**4**(Ala). In contrast, complexes of **1′**–L-**6**(Ala) and **1′**–D-**6**(Ala), supported by the two-point coordination (Figure 5), produce only smaller energy difference ($\Delta E_{D-L} = ca.$ −0.5 kcal mol^{-1}). Thus, energetic advantage of the three-point binding for chiral discrimination is also proven in the DFT-based simulations.

In addition, ΔE_{add} and $\Delta E_{1'}$ values for **1′**–**4**(Ala), similarly employed in the preceding section, were estimated to be about 2.8 and 0.4 kcal mol^{-1}, respectively. Thus the clear difference in energies of D-/L-complexes (ΔE_{D-L}) might originate from conformational advantage of the L-additive in the three-point binding to the 3_{10}-helical N-terminus. These results support the preceding AM1[7]-derived conclusions.

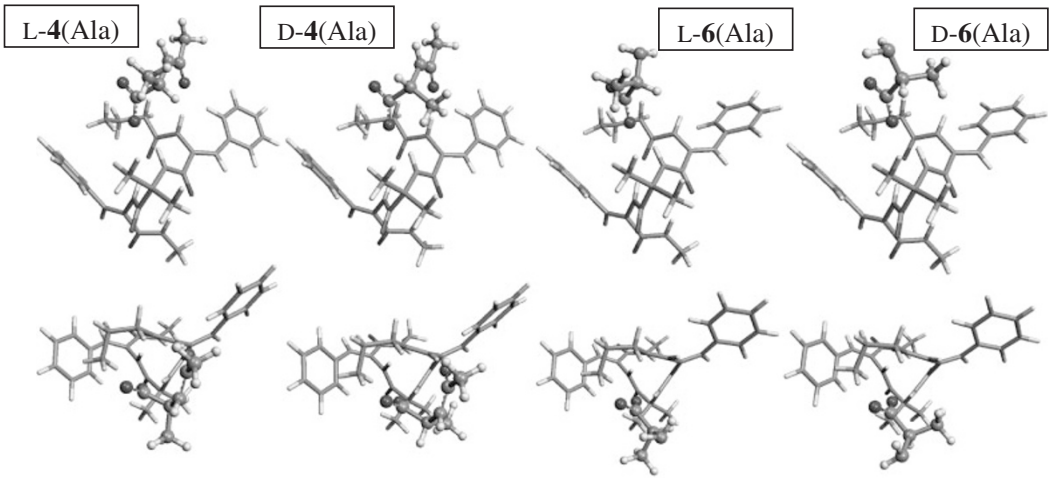

Figure 5. Complex structures of peptide **1**′ with L-/D-**4**(Ala) or L-/D-**6**(Ala), obtained from the B3LYP/6-31G(d,p)-based optimization.[8,9] View from the N-terminus is also shown in the corresponding bottom.

Table I. Structure parameters predicted for the complex of peptide **1**′ (or **1**) with L-**4**(Ala) or D-**4**(Ala) by the B3LYP/6-31G(d,p) method[8,9] or by the AM1 method[7]

intermolecular parameters	B3LYP/6-31G(d,p)		AM1[a]	
peptide **1**′ or **1**/**4**(Ala)	**1**′/L-**4**	**1**′/D-**4**	**1**/L-**4**	**1**/D-**4**
ammonium/carboxylate				
N···C (Å)	3.0	3.0	3.1 (3.1)	3.1 (3.1)
NH Δ^ZPhe(2)/CO acetyl				
H···O (Å)	1.9	1.9	2.2 (2.2)	2.2 (2.2)
N–H···O (deg)	170	169	136 (137)	135 (136)
H···O=C (deg)	150	157	164 (163)	170 (168)
NH Aib(3)/CO carboxylate				
H···O (Å)	1.9	1.9	2.1 (2.1)	2.1 (2.1)
N–H···O (deg)	161	162	150 (150)	150 (150)
H···O=C (deg)	136	143	122 (121)	128 (127)
H(N) Δ^ZPhe(2)···H(C^α) Ala (Å)	2.8	4.7	3.2 (3.3)	5.3 (5.3)
H(N) Aib(3)···H(C^α) Ala (Å)	2.8	4.4	2.6 (2.5)	4.2 (4.2)
intramolecular torsion angle (deg)[20]				
4: Ala ϕ	−65	−56	−67 (−72)	−58 (−61)
1′ or **1**: β-Ala(1) θ/ψ	73/−154	72/−152	66/−176 (66/−175)	66/−175 (66/−174)
Δ^ZPhe(2) ϕ/ψ	−52/−33	−51/−35	−33/−45 (−33/−45)	−32/−45 (−31/−47)
χ^1/χ^2	−2/12	−2/12	−1/−48 (0/52)	−1/−48 (0/52)
Aib(3) ϕ/ψ	−61/−22	−63/−20	−47/−43 (−46/−44)	−47/−44 (−46/−45)
Δ^ZPhe(4) ϕ/ψ	−65/−13	−68/−11	−34/−36 (−35/−37)	−35/−36 (−35/−37)
χ^1/χ^2	−7/−40	−7/−41	−2/−42 (−2/−42)	−2/−43 (−2/−43)

[a]Values without or with the parentheses correspond to structures from left-side or right-side column of Figure 3, respectively, where the Δ^ZPhe(2,6,8)'s side-chain orientations (χ^2) are essentially different.

CONCLUSIONS

The MO computations have demonstrated that, in each amino acid species, the three-point coordination shows the tendency to generate larger difference in energies of D-/L-complexes than the two-point type. The theoretical prediction is fully consistent with

our previous findings, in which preferential induction of right-handed helix in peptide **1** occurs with *N*-carbonyl protected L-amino acid, but inefficiently with simple carboxylic acid.[2a] In the three-point binding, negative ϕ values of *N*-carbonyl-blocked L-amino acid species are suggested to be a key conformer for the preferential fitting to induce right-handed helix through the noncovalent chiral interaction. The energetic advantage for the three-point binding, as generally approved,[4] implies the function of 3_{10}-helical N-terminus to recognize the chirality of *N*-carbonyl-blocked amino acid molecule.

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