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A Revised Conformational Code for the Exhaustive Analysis of Conformers with One-to-One Correspondence between Conformation and Code: Application to the VCD Analysis of (*S*)-Ibuprofen

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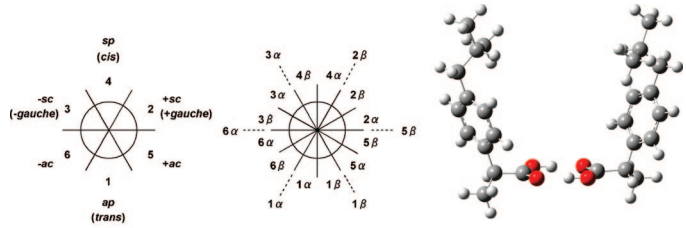

***ibup*-3α2ασ3ασ2α(*ibup*-3α2ασ3ασ2α)**

A revised conformational code for the exhaustive analysis of conformers of all classes of molecules is proposed and applied to the vibrational circular dichroism (VCD) analysis of (*S*)-ibuprofen. The revised code can strictly define the conformation of compounds with relatively high-symmetry substituents and is especially useful for visualizing conformational changes in ligands and proteins. The conformational analysis of (*S*)-ibuprofen using the code in the solution state reveals that the four energetically preferred conformations, ***ibut*-3α2ασ(*phpa*-3ασ2α)**, ***ibut*-3α2ατ(*phpa*-3ατ2α)**, ***ibut*-2β3βτ(*phpa*-3ατ2α)**, and ***ibut*-2β3βσ(*phpa*-3ασ2α)**, exist in the monomer and dimer forms. In $CDCl_3$ solution, the dimer form is stabilized as the "U"-shape, and the ease of crystallization is largely ascribed to the conformation of ***phpa*-3α2α** for (*S*)-ibuprofen. The new version of the conformational code has the possibility to be used as a tool for the exhaustive analysis of conformers of all kinds of chemical compounds, conformome analysis, and in the future for metabolome, proteome, and genome analyses.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs),[1] including ibuprofen, inhibit the cyclooxygenase enzymes (COX-1 and COX-2) from producing prostaglandins.[2] The COX enzymes are heme-containing membrane proteins with molecular mass of 70 000. It has been revealed that time-dependent and time-independent ligands elicit nearly identical enzyme conformations in the membrane proteins.[2b]

Human Serum Albumin (HSA) is an abundant plasma protein that binds a remarkably wide range of endogenous ligands including nonesterified fatty acids, bilirubin, hemin, and thyroxine.[3] Many drugs with acidic or electronegative properties, such as ibuprofen, also bind to HSA. The analysis of conformational changes in HSA is also very important in order to better understand problems associated with adsorption, distribution, metabolism, and elimination (ADME).[3]

A gene can be represented by the expression of the base sequence of nucleic acids such as A (adenine), T (thymine), G (guanine), and C (cytosine), whereas a primary structure of

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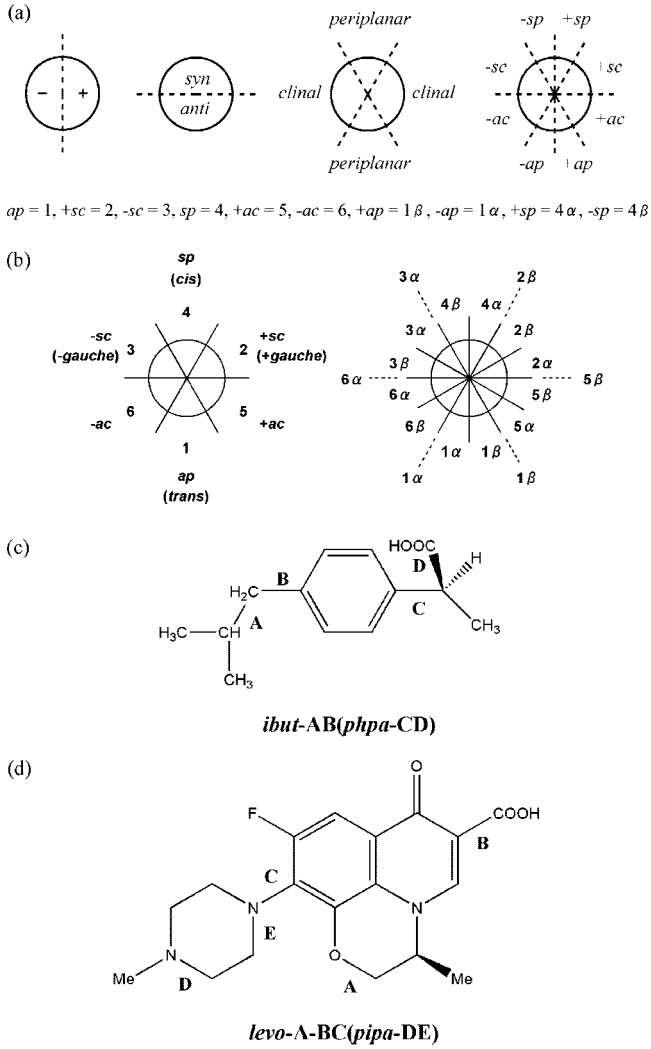

FIGURE 1. (a) Classification of dihedral angles for conformational representation according to IUPAC nomenclature.[4] (b) Classification of dihedral angles for revised conformational elements. (c) Chemical structure and representation of conformational code for (*S*)-ibuprofen. (d) Chemical structure and representation of conformational code for levofloxacin.

protein can be expressed by the code list of the amino acids such as GLY, ALA, and VAL. These codes enable us to carry out the exhaustive analysis of genes (genome) or proteins (proteome). At present, however, there are no, internationally accepted, common codes for the exhaustive analysis of the 3D conformational information for all kinds of chemical compounds, including those for metabolome analysis.

Recently, we have introduced an expansion of IUPAC nomenclature (Figure 1a)[4] to describe the conformations of large molecules using a new conformational code. The code emerged from a conformational analysis required to calculate and interpret the vibrational circular dichroism (VCD)[5] spectra associated with the chiral core of the anticancer drug paclitaxel (Taxol), baccatin III.[6] This code was also useful for describing which parts of a molecule contribute to conformational change and how conformations change in membrane proteins and ligands.

However, IUPAC Rules for Nomenclature of Organic Chemistry Rule E-5.6[4] was subsequently found to be unfavorable for applying certain aspects of the code. In particular, the preliminary code did not always have a one-to-one correspondence between conformation and code when all the groups or atoms are the same and the group or atom with the smallest torsion angle is selected.[6]

In this paper, we describe two such ambiguous cases, ibuprofen and levofloxacin, both of which contain relatively high-symmetry substituents, and propose a revised conformational code that resolves the earlier lack of complete specificity. We also present the details of the conformational analysis of (*S*)-ibuprofen using VCD as an illustrative application of the revised code.

Results and Discussion

Conformational Code: Rule 1. The classification of conformational elements based on the IUPAC Rules for Nomenclature of Organic Chemistry Rule E-5.6[4] has not been divided equally (Figure 1a). In the former paper,[6] we introduced the conformational elements 1β (+*ap*), 1α (−*ap*), 4α (+*sp*), and 4β (−*sp*), because two conformations can be optimized in the same region as for *ap* (1) and *sp* (4) by theoretical calculations occasionally (Figure 1a). However, similar situations can occur as for +*sc* (2), −*sc* (3), +*ac* (5), and −*ac* (6). Further, the definition of the borders had not been decided. The classification of conformational elements according to the IUPAC Rules for Nomenclature of Organic Chemistry Rule E-5.6[4] is based on plus (0° to 180°) and minus (0° to −180°). A molecular structure is deeply related to the symmetry. As a result, we propose a choice of borders and a classification of conformational elements 1−6 with α (clockwise) or β (counterclockwise) as shown in Figure 1b.

There are two types of different nomenclatures (Figure 1b): one is the Klyne−Prelog convention (±*ap*, ± *sp*, ± *ac*, and ± *sc*), and spectroscopists commonly use a different nomenclature (*trans*, +*gauche*, and −*gauche*).[7] The proposed conformational code can integrate the different nomenclatures seamlessly, and is especially useful for the homology analysis of conformers for large entire molecules such as membrane proteins. On the other hand, the IUPAC codes with α (clockwise) and β (counterclockwise) such as +*sc*α are convenient for the scientific discussion of the conventional local conformations.

Conformational Code: Rule 2. In (*S*)-ibuprofen, the ortho-position hydrogens of the aromatic ring with respect to the isobutyl group cannot be distinguished (Figure 1c). In this case,

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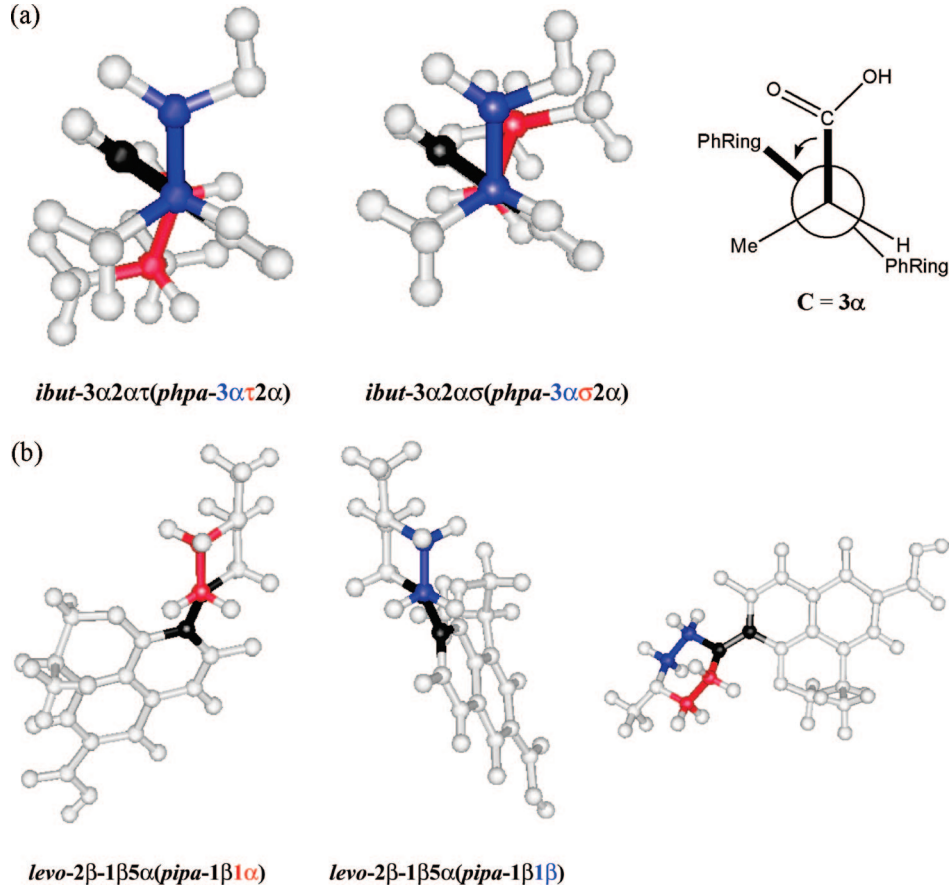

FIGURE 2. (a) Case that a conformational code corresponds to two conformations [(*S*)-ibuprofen]. The conformational element of angle location **C** is determined by the dihedral angle between the blue and black bonds (**3α**) and by the relative positional relationship between the blue and red bonds (***τ*** or ***σ***). (b) Case that a conformation has two conformational codes (levofloxacin). The conformational element of angle location **E** is determined by the dihedral angle between the blue and black bonds (**1*β***) according to the priory rule of plus angle.

a single conformational code corresponds to two conformations. For example, ***ibut*-3α2α(*phpa*-3α2α)** corresponds to two conformations (Figure 2a). In such cases, new codes, σ (cis) and τ (trans), are introduced, and these codes are used based on the relative positional relationship of two focused bonds (the blue and red bonds in Figure 2a).

Conformational Code: Rule 3. In levofloxacin, the 4-methylpiperazinyl group has a reflection plane (Figure 1d). The conformational codes ***levo*-2*β*-1*β*5α(*pipa*-1*β*1*β*)** and ***levo*-2*β*-1*β*5α(*pipa*-1*β*1α)** represent the same conformation because the absolute values of the angles are same with different signs for the selection of the smallest torsion angle (Figure 2b). In such a case, the plus angle has priority, and then the conformation is represented as the conformational code ***levo*-2*β*-1*β*5α(*pipa*-1*β*1*β*)**.

As reference for these new rules, the entire statement of the revised conformational code is provided in the Supporting Information.[8]

Conformational Analysis of (*S*)-Ibuprofen. First, the conformational search of (*S*)-ibuprofen monomer was carried out by using density functional theory (DFT) calculations.[9] On the basis of the optimization of parts for (*S*)-ibuprofen, 22 conformations were selected, and then 10 conformations were optimized as the population-rich species.[8] The difference of Gibbs free energy between conformations ***ibut*-3α2α** and ***ibut*-2*β*3*β*** was very small, on the other hand, the difference of Gibbs free energy among conformations ***phpa*-3α2α** and ***phpa*-3*β*6α** was large (Figure 3). The 4 conformations ***ibut*-3α2ασ(*phpa*-3ασ2α)**, ***ibut*-3α2ατ(*phpa*-3ατ2α)**, ***ibut*-2*β*3*β*τ(*phpa*-3ατ2α)**, and ***ibut*-2*β*3*β*σ(*phpa*-3ασ2α)** accounted for greater than 86% of the calculated population distribution.[8] Interestingly, the predicted VCD spectra of ***ibut*-3α2ασ(*phpa*-3ασ2α)**, ***ibut*-3α2ατ(*phpa*-3ατ2α)**, ***ibut*-2*β*3*β*τ(*phpa*-3ατ2α)**, and ***ibut*-**

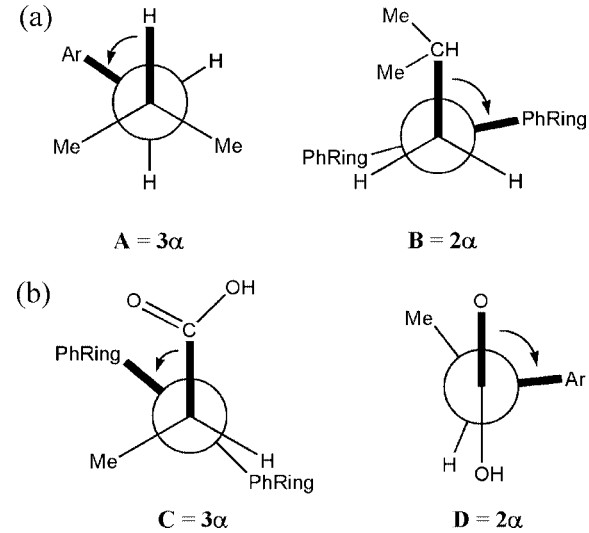

FIGURE 3. (a) Dihedral angles at angle locations of ***ibut*-3α2α**. (b) Dihedral angles at angle locations of ***phpa*-3α2α**.

(8) See the Supporting Information.

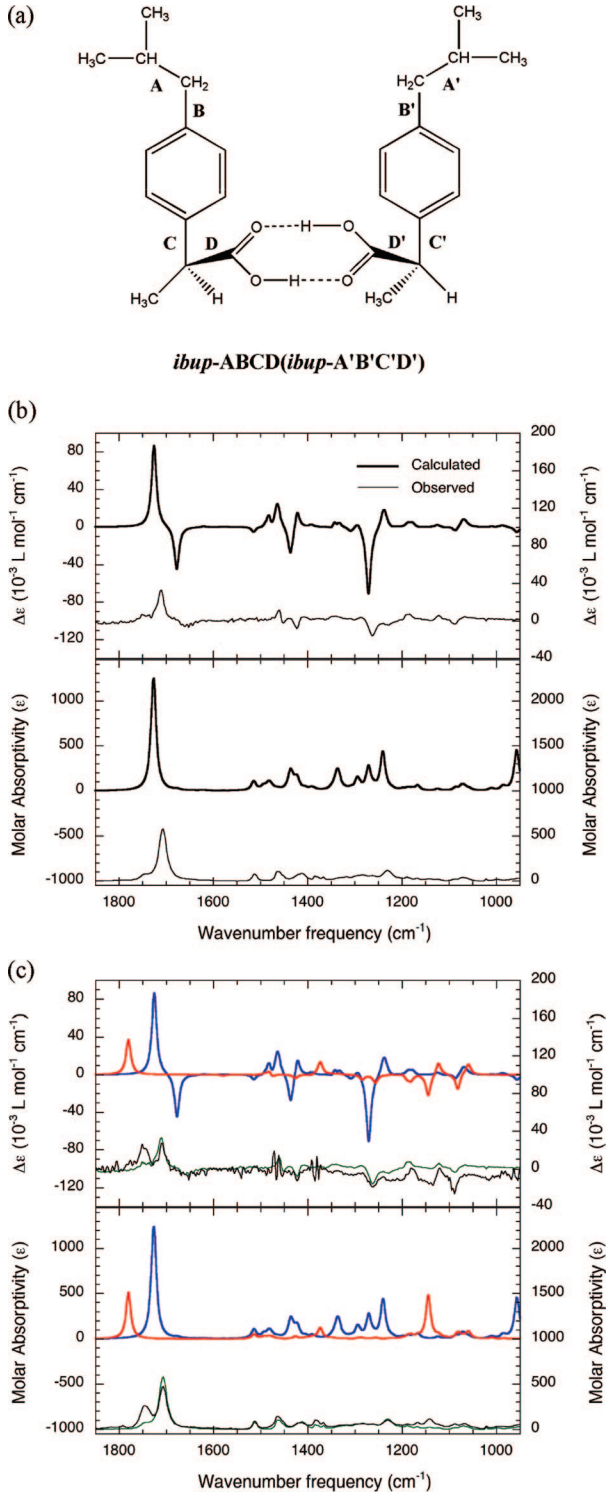

FIGURE 4. (a) Chemical structure and representation of the conformational code for (*S*)-ibuprofen dimer. (b) Comparison of the measured VCD ($\Delta\epsilon$) and IR (ϵ) spectra of (*S*)-ibuprofen (thin: $CDCl_3$, 0.21 M, BaF_2, 72 μm path length) with the predicted (population weighted) spectra of 16 energetically preferred conformations for (*S*)-ibuprofen dimer (bold: B3LYP/6-31G*). (c) Comparison of the measured VCD ($\Delta\epsilon$) and IR (ϵ) spectra of (*S*)-ibuprofen (green: $CDCl_3$, 0.21 M, BaF_2, 72 μm path length; black: $CDCl_3$, 0.008 M, BaF_2, 491 μm path length) with the predicted (population weighted) spectra of energetically preferred conformations for (*S*)-ibuprofen dimer (blue: 16 conformations, B3LYP/6-31G*) and (*S*)-ibuprofen monomer (red: 4 conformations, B3LYP/6-31G*). The noise ($\Delta\epsilon$) spectrum of (*S*)-ibuprofen in the dilute solution ($CDCl_3$, 0.008 M, BaF_2, 491 μm path length) is included in the Supporting Information.[8]

***2β3βσ*(*phpa*-3α*σ*2α)** were very similar, whereas the predicted VCD spectra of ***ibut*-3α2α*σ*(*phpa*-3α*σ*2α)** and ***ibut*-3α2α*σ*(*phpa*-3*β*σ6α)** were not.[8] The VCD band shape is largely influenced by the conformational variations of ***phpa*-CD**.

In $CDCl_3$, dimers of carboxylic acids are easily formed by intermolecular H-bonding of two carboxyl groups.[10] The conformational search of (*S*)-ibuprofen dimer was also carried out by using density functional theory calculations.[9] As shown in Figure 4a, the representation of conformational code for (*S*)-ibuprofen dimer was defined as ***ibup*-ABCD(*ibup*-A′B′C′D′)**. On the basis of the monomer calculation, 26 conformations were selected.[8] The 16 conformations within 1 kcal mol^{-1} of ΔG accounted for greater than 86% of the calculated population distribution.[8] As in the case of monomer, conformations ***ibup*-AB3α2α(*ibup*-A′B′3α2α)** were apt to be more stable than ***ibup*-AB3*β*6α(*ibup*-A′B′3α2α)**.[8] In comparison with the previous VCD analyses of pharmaceutical compounds thalidomide[5f] and baccatin III,[6] the number of conformations within 1 kcal mol^{-1} of ΔG was large. This may affect the low selectivity against COX-1 and COX-2.[2]

The measured VCD and IR spectra of (*S*)-ibuprofen ($CDCl_3$, 0.21 M, BaF_2, 72 μm path length) were found to be in fairly good agreement with the population weighted VCD and IR spectra of the 16 energetically preferred conformations for (*S*)-ibuprofen dimer (Figure 4b). On the other hand, the new ν_{CO} VCD band of (*S*)-ibuprofen with other new bands was observed in the dilute $CDCl_3$ solution (Figure 4c). These new bands including the IR bands corresponded closely to the population weighted bands of the 4 energetically preferred conformations for (*S*)-ibuprofen monomer. Due to the similarity among the predicted VCD spectra for the lowest energy conformers, the experimental VCD spectrum cannot be used to distinguish between the case where the distribution is dominated by one of the conformers and that where the four lowest energy minima are equally populated. However, the conformations ***ibut*-3α2α** and ***ibut*-2*β*3*β*** have a symmetry relationship locally, and the difference of Gibbs free energy between two conformations is very small. It is suggested that the four energetically preferred conformations, ***ibut*-3α2α*σ*(*phpa*-3α*σ*2α)**, ***ibut*-3α2α*τ*(*phpa*-3α*τ*2α)**, ***ibut*-2*β*3*β**τ*(*phpa*-3α*τ*2α)**, and ***ibut*-2*β*3*β**σ*(*phpa*-3α*σ*2α)**, exist in the monomer and dimer forms in the solution state. Further tight variations in the conformational distribution cannot be assessed. The measured VCD and IR spectra of (*S*)-ibuprofen in a DMSO-d_6 solution were quite different from those of (*S*)-ibuprofen in the dilute $CDCl_3$ solution, and were in relatively good agreement with the calculated monomer spectra in consideration of a solvent effect.[8] It is suggested that the monomer forms of (*S*)-ibuprofen with a solvent effect exist in the DMSO-d_6 solution.

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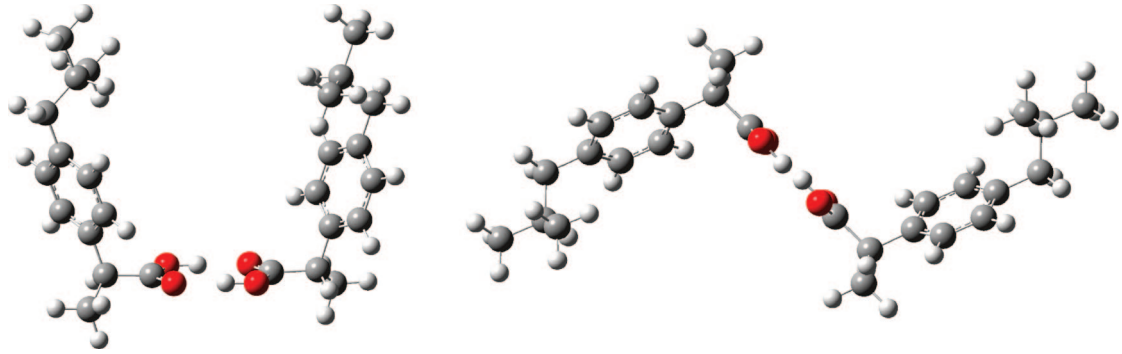

FIGURE 5. Comparison of the optimized geometry of ***ibup*-3α2ασ3ασ2α(*ibup*-3α2ασ3ασ2α)** (left: B3LYP/6-31G*) with the geometry of ***ibup*-3α2ασ3βσ6α(*ibup*-3α2ασ3ασ2α)** (right: B3LYP/6-31G*).

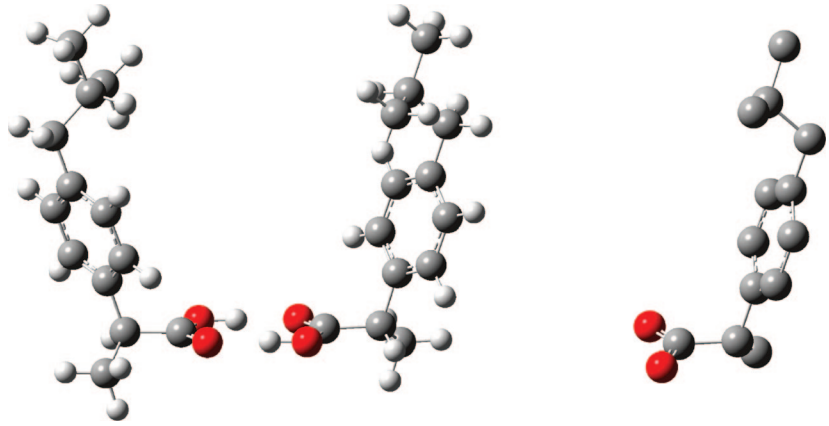

FIGURE 6. Comparison of the optimized geometry of ***ibup*-3α2ασ3ασ2α(*ibup*-3α2ασ3ασ2α)** (B3LYP/6-31G*) with the geometry of ***ibut*-A2ασ(*phpa*-3βσ2α)** for 1EQG.[2b,12]

Conformational analyses of ibuprofen in the solid state by using other techniques have been reported.[11] The conformation of ibuprofen monomer in the crystal structure closely resembles that of ***ibut*-3α2ατ(*phpa*-3ατ2α)**.[11f] However, the conformational shape of the ibuprofen dimer-unit in the crystal structures looks like an "*N*"-shape and resembles that of unstable ***ibup*-3α2ασ3βσ6α(*ibup*-3α2ασ3ασ2α)** (Figure 5).[11b,d,e] To the best of our knowledge, the report of the crystal structure for the enantiomers of ibuprofen was not found. The "*N*"-shape has an advantage for the crystal packing, and only the racemic mixture can stabilize the "*N*"-shape. In $CDCl_3$ solution, the dimer form of (*S*)-ibuprofen is stabilized as the "U"-shape. The ease of crystallization is largely ascribed to the conformation of ***phpa*-3α2α** for (*S*)-ibuprofen.

The proposed conformational code is especially useful for the comparison of the calculated conformations with the X-ray structures of ligands incorporated with proteins. In the COX-1 enzyme, 1EQG (PDB ID),[2b,12] two molecules of (*S*)-ibuprofen were incorporated, and both molecules were represented as ***ibut*-A2ασ(*phpa*-3βσ2α)**. These conformations resembled one of the optimized structures (Figure 6). On the other hand, 4 molecules of (*S*)-ibuprofen were contained for Human Serum Albumin, 2BXG,[3,12] and 3 different conformations, ***ibut*-A2βτ(*phpa*-5βτ4α)**, ***ibut*-A4ατ(*phpa*-3βτ2β)**, and ***ibut*-A2ατ(*phpa*-3βτ2β)**, existed. These conformations were also different from the optimized stable conformations. The difference in conformations for the ligands seems to be related to the functions of the proteins.

Conclusions

In the present study, a new revised conformational code is proposed using the vibrational circular dichroism (VCD) study of (*S*)-ibuprofen in the solution state. The four lowest energy minima, ***ibut*-3α2ασ(*phpa*-3ασ2α)**, ***ibut*-3α2ατ(*phpa*-3ατ2α)**, ***ibut*-2β3βτ(*phpa*-3ατ2α)**, and ***ibut*-2β3βσ(*phpa*-3ασ2α)**, exist in the monomer and dimer forms. In $CDCl_3$ solution, the dimer form is stabilized as the "U"-shape. The "*N*"-shape has an advantage for the crystal packing, and the ease of crystallization is largely ascribed to the conformation of ***phpa*-3α2α** for (*S*)-ibuprofen. The new version of the conformational code can be applied to all chemical compounds with relatively high-symmetry substituents. At present, there are no tools to exhaustively analyze a conformational change of proteins such as rhodopsin. The revised conformational code has the possibility to be used as a tool for the exhaustive analysis of conformers of all kinds of chemical compounds, conformome analysis, and in the future for metabolome, proteome, and genome analyses.

Experimental Section

Measurements. All reagents were of commercial grade. The infrared and VCD spectra were recorded on a commercial Fourier

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transform VCD spectrometer from BioTools, Inc. The VCD spectra of the solution state were recorded with 4−5 h data collection time at 4 cm^{-1} resolution. The $CDCl_3$ solutions were placed in a 72 or 491 μm path length cell with BaF_2 windows. In the VCD spectra of the solution state, the raw VCD spectra of the solvents were subtracted.

Calculations. All geometry optimizations, conformer searches, vibrational frequencies, and absorption and VCD intensities for (*S*)-ibuprofen monomer and dimer were calculated with the Gaussian 03 program[9] on a Pentium 4 (3.2 GHz) PC. Density functional theory with B3LYP functional and 6-31G(d) basis set was used for the calculations. The theoretical absorption and VCD spectra were simulated with Lorentzian band shapes and 6 cm^{-1} full width at half-height. The ab initio frequencies were scaled by 0.97, and the thermal corrections to Gibbs free energies were scaled with 0.9989.

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Supporting Information Available: Entire statement of revised conformational code; relative Gibbs free energies and populations of conformations for the (*S*)-ibuprofen monomer and dimer; Cartesian coordinates of ***ibut*-3α2α*σ*(*phpa*-3α*σ*2α)**, ***ibut*-3α2α*τ*(*phpa*-3α*τ*2α)**, ***levo*-2*β*-1*β*5α(*pipa*-1*β*1*β*)**, ***ibup*-3α2α*σ*3α*σ*2α(*ibup*-3α2α*σ*3α*σ*2α)**, and ***ibup*-3α2α*σ*3*β*σ6α(*ibup*-3α2α*σ*3α*σ*2α)**; comparison of the optimized geometry of ***ibup*-3α2α*σ*3α*σ*2α(*ibup*-3α2α*σ*3α*σ*2α)** with the geometry of ***ibut*-A2*βτ*(*phpa*-5*βτ*4α)** for 2BXG; VCD and IR spectra of (*S*)-ibuprofen in $CDCl_3$ and DMSO-d_6 with noise spectra; and VCD and IR spectra calculated for each conformation of (*S*)-ibuprofen monomer and dimer. This material is available free of charge via the Internet at http://pubs.acs.org.

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