

## Direct Observation of Odd–Even Effect for Chiral Alkyl Alcohols in Solution Using Vibrational Circular Dichroism Spectroscopy

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**Abstract:** The odd–even effect of chiral alkyl alcohols, (S)-CH<sub>3</sub>CHOHC<sub>n</sub>H<sub>2n+1</sub> ( $n = 2–8$ ), in solution state has been observed spectroscopically for the first time. The vibrational circular dichroism (VCD) bands at 1148 cm<sup>-1</sup> exhibit a clear odd–even effect. The observed VCD bands of (R)-(–)-2-hexanol correspond well to those predicted (population weighted). Density functional theory calculations indicate that the most prevalent conformations in solution are the all-*trans* forms. The odd–even effect of the VCD bands is ascribed to the alternating terminal methyl motions in the alkyl chains relative to fixed motions near the chiral center in the *trans* conformations. The conformational sensitivity of VCD for the chiral alcohols in the solution state may be useful for the design of liquid crystals and ligands in the future.

### Introduction

In nature, effects of odd–even carbon number in alkyl chains of organic compounds exist in many areas of chemical applications. One example is volatile organic compounds (VOCs). VOCs are an important reactive component of the continental and marine atmosphere and play a major role in affecting levels of gaseous oxidants such as O<sub>3</sub> and H<sub>2</sub>O<sub>2</sub>. The odd/even *n*-alkane ratios have been utilized to examine the origin of VOCs.<sup>1</sup> Odd–even effects of alkyl chains have also been applied to light-emitting diodes (LED),<sup>2</sup> self-assembled monolayers,<sup>3</sup> liquid crystals,<sup>4</sup> and drag-reducing surfactants<sup>5</sup> in the field of materials science. These effects in the aggregated or solid state are observed by sum frequency generation (SFG),<sup>6</sup> low-frequency Raman,<sup>7</sup> solid-state <sup>13</sup>C nuclear magnetic resonance (NMR),<sup>8</sup> or circular dichroism (CD)<sup>9</sup> spectroscopy. In solution state, however, no such effects are ordinarily observed.<sup>10</sup>

The difference of even and odd alkyl chains in the solid state is ascribed to the difference of the packing in crystal structure.<sup>7</sup>

In the solution state, alkyl chains take various conformations, and this obstructs the application of odd–even effects in solution. However, the extension of odd–even effects to the solution state has been vigorously pursued.<sup>2</sup> These odd–even effects in solution are unclear and have not been theoretically examined. Recently, high antitumor activities of Annonaceous acetogenins containing chiral alkyl alcohol units and their molecular design have been reported.<sup>11</sup> The conformational preferences of chiral alcohols in the solution state have also been attracting considerable interest as a model for the O–C–C–C unit in C-glycosides.<sup>12</sup> Vibrational circular dichroism (VCD) spectroscopy<sup>13</sup> is a new technique to obtain conformational information of chiral molecules. VCD is the extension of electronic CD into the infrared region where fundamental transitions occur. All vibrational motions of the molecules (3*N*–6 for a molecule of *N* atoms) are chromophores in the electronic CD sense. VCD has also been used to great advantage to study the solution conformations of large biological molecules including proteins, nucleic acids, and sugars.<sup>14</sup> The VCD spectra are very sensitive to the conformations of chiral molecules. This

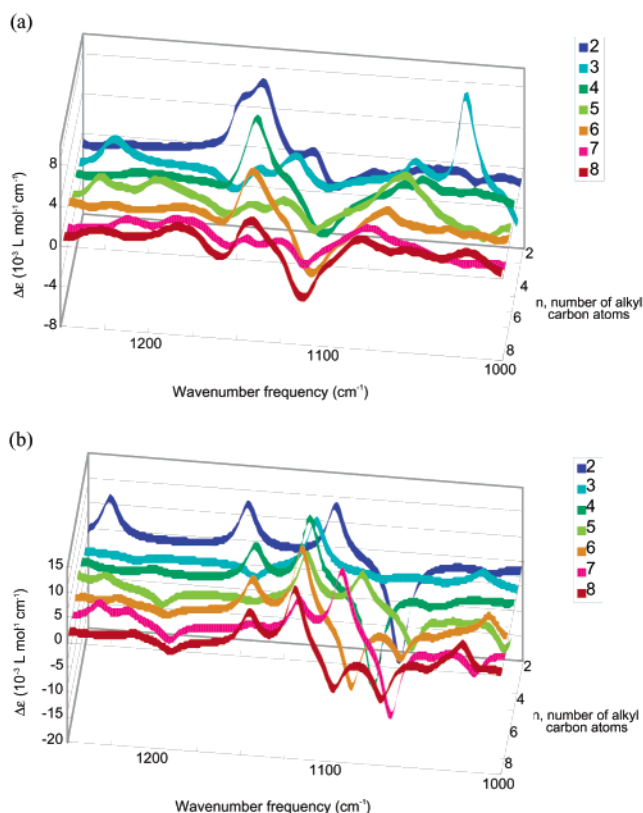
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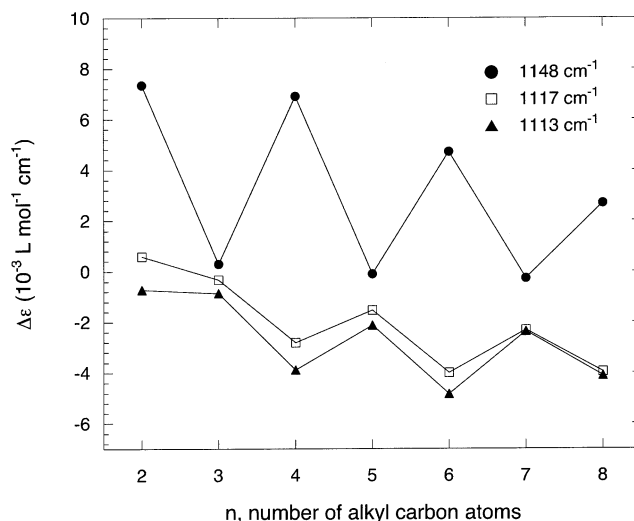


**Figure 1.** Odd–even effect of  $(S)\text{-CH}_3\text{CHOHC}_n\text{H}_{2n+1}$  ( $n = 2\text{--}8$ ) in VCD bands. (a) VCD spectra of  $(S)\text{-CH}_3\text{CHOHC}_n\text{H}_{2n+1}$  ( $n = 2\text{--}8$ ;  $\text{CCl}_4$ , 2.0–3.6 M, 73  $\mu\text{m}$  path length). (b) Predicted VCD spectra of all-*trans* conformations for  $(S)\text{-CH}_3\text{CHOHC}_n\text{H}_{2n+1}$  ( $n = 2\text{--}8$ ; B3LYP/6-31G\*; calculated by using the values of *R*-forms).

suggests that VCD spectroscopy has a potential for application to devices for stereochemistry analysis as well as X-ray crystallography and NMR spectroscopy. Here, we demonstrate that an odd–even effect for a series of chiral alcohols ( $\text{CH}_3\text{-CHOHC}_n\text{H}_{2n+1}$ ;  $n = 2$ , **But**;  $n = 3$ , **Pen**;  $n = 4$ , **Hex**;  $n = 5$ , **Hep**;  $n = 6$ , **Oct**;  $n = 7$ , **Non**;  $n = 8$ , **Dec**) in solution can be observed by using VCD spectroscopy and can be theoretically interpreted in terms of conformations and molecular motions.

## Results and Discussion

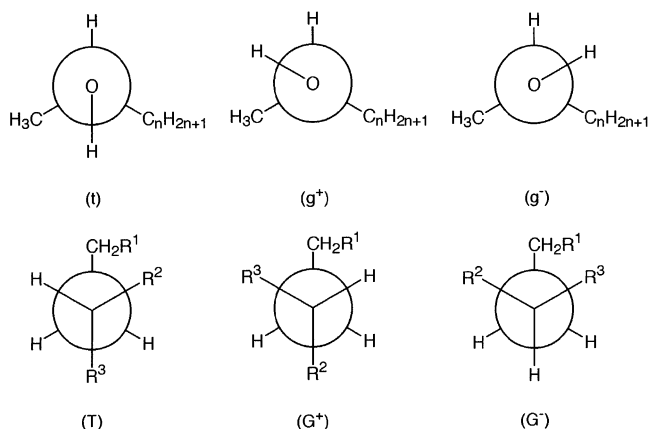
Figure 1a shows the VCD spectra of  $(S)\text{-CH}_3\text{CHOHC}_n\text{H}_{2n+1}$  ( $n = 2\text{--}8$ ;  $\text{CCl}_4$ , 2.0–3.6 M, 73  $\mu\text{m}$  path length). The odd–even effect in the solution state has been observed spectroscopically for the first time in the VCD bands at 1148  $\text{cm}^{-1}$  (Figure 2). At 1117 and 1113  $\text{cm}^{-1}$ , weak odd–even effects have also been found (Figure 2). The odd–even effect of the VCD bands at 1148  $\text{cm}^{-1}$  has also been observed at dilute concentrations.<sup>15</sup> These alcohols indicate the odd–even effect not only in solution state but also in liquid state. Even in aqueous solution, the VCD band at 1148  $\text{cm}^{-1}$  has been observed for  $(S)\text{-But}$ .<sup>15</sup> The absorption bands near 1150  $\text{cm}^{-1}$  separate at the dilute concentrations [ $(S)\text{-Pen}$ , 0.10 M;  $(S)\text{-Oct}$ , 0.06 M], and one of the absorption bands does not shift.<sup>15</sup> In the VCD and IR spectra of the alkyl alcohols, there are two types of bands; one is strongly affected by the intermolecular hydrogen bonding and



**Figure 2.** Plots of VCD intensities ( $\Delta\epsilon$ ) (1148, 1117, and 1113  $\text{cm}^{-1}$ ) vs the number of alkyl carbon atoms in  $(S)\text{-CH}_3\text{CHOHC}_n\text{H}_{2n+1}$  ( $n = 2\text{--}8$ ).

the other is not. Polavarapu and co-workers have already reported the VCD of  $(R)\text{-But}$  at different concentrations and the influence of intermolecular hydrogen bonding.<sup>16</sup> They have shown that the VCD band at 1156  $\text{cm}^{-1}$  is assigned as  $\text{C}^*\text{-C-H}$  bending, and the other at 1143  $\text{cm}^{-1}$  is assigned as  $\text{C}^*\text{-O}$  stretching and  $\text{C}^*\text{-C-H}$  bending. These findings suggest that there is the influence of intermolecular hydrogen bonding, but the VCD bands at 1148  $\text{cm}^{-1}$  are ascribed to the isolated molecules but not to the strong-hydrogen-bonding structures such as dimer formation.

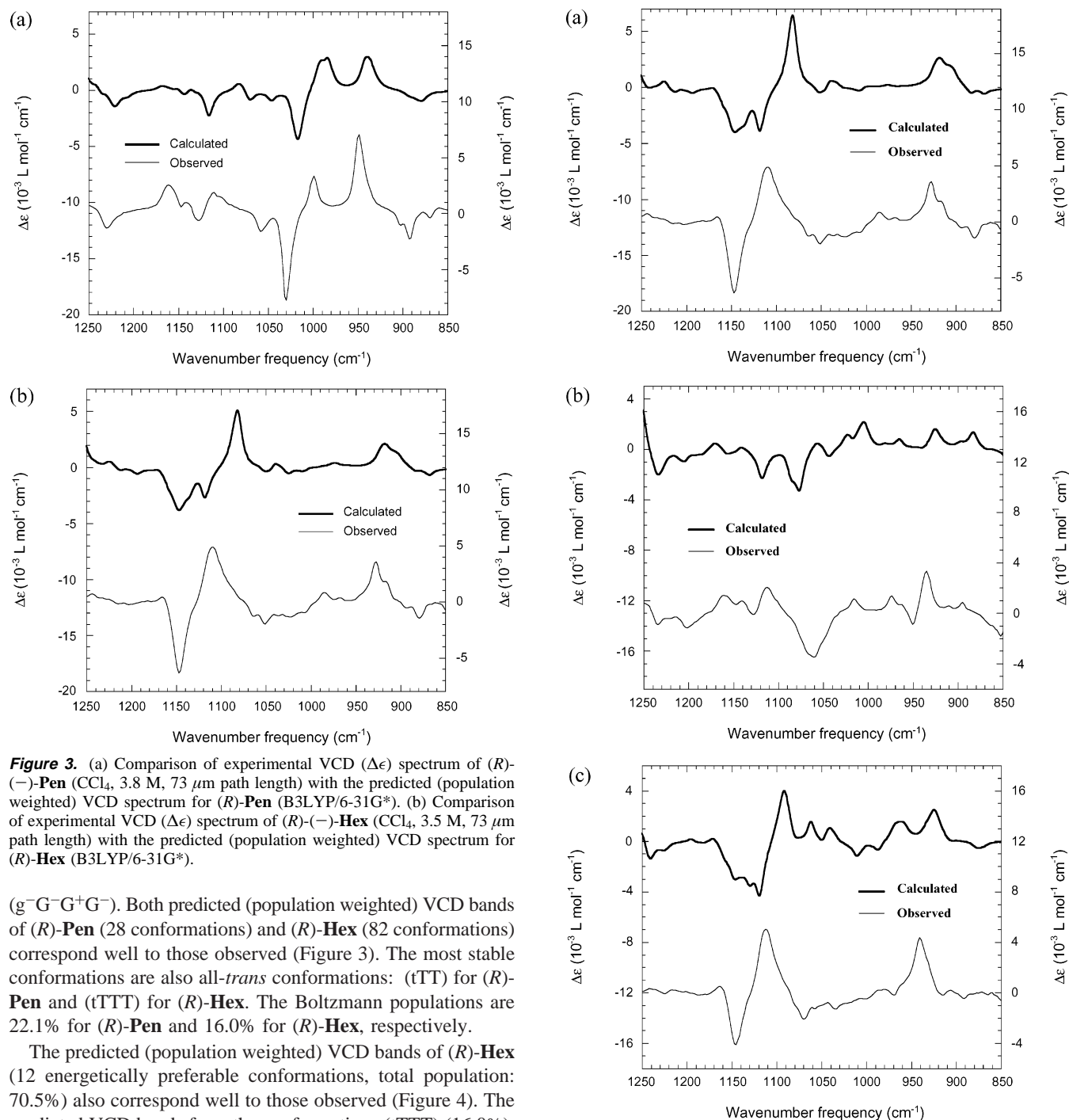
To reveal the odd–even effects, the conformational and vibrational analyses of chiral alcohols,  $(R)\text{-CH}_3\text{CHOHC}_n\text{H}_{2n+1}$  ( $n = 2\text{--}8$ ), were carried out using density functional theory calculations.<sup>17</sup> Polavarapu and co-workers have also reported the predominant conformations of  $(R)\text{-But}$ .<sup>16</sup> For  $(R)\text{-But}$ , the most stable conformation is (tT), and the Boltzmann population from the predicted Gibbs free energy is 28.9%. We have extended their calculations and found 28 conformations for  $(R)\text{-Pen}$  and 82 conformations for  $(R)\text{-Hex}$ .<sup>15</sup> For  $(g^+g^+g^-)$  in  $(R)\text{-Pen}$ , two of the distorted conformations are found. The conformations (tTG<sup>+</sup>G<sup>+</sup>), (tG<sup>+</sup>G<sup>+</sup>T), (g<sup>+</sup>G<sup>+</sup>G<sup>+</sup>T), (g<sup>+</sup>G<sup>+</sup>G<sup>+</sup>G<sup>+</sup>), (g<sup>+</sup>TG<sup>+</sup>T), (g<sup>+</sup>TG<sup>+</sup>G<sup>+</sup>), and (g<sup>+</sup>G<sup>+</sup>G<sup>+</sup>G<sup>+</sup>) also have two distorted ones for  $(R)\text{-Hex}$ . On the other hand, no stable conformations of  $(R)\text{-Hex}$  are optimized for (tG<sup>+</sup>G<sup>+</sup>G<sup>+</sup>), (tG<sup>+</sup>G<sup>+</sup>G<sup>+</sup>G<sup>+</sup>), (g<sup>+</sup>G<sup>+</sup>G<sup>+</sup>G<sup>+</sup>), (g<sup>+</sup>G<sup>+</sup>G<sup>+</sup>G<sup>+</sup>G<sup>+</sup>), (g<sup>+</sup>G<sup>+</sup>G<sup>+</sup>G<sup>+</sup>G<sup>+</sup>), and



$R^1 = \text{alkyl or H}$ ,  $R^2 = \text{OH or H}$ ,  $R^3 = \text{methyl or hydroxyalkyl}$

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(15) See Supporting Information.



**Figure 3.** (a) Comparison of experimental VCD ( $\Delta\epsilon$ ) spectrum of (*R*)-(-)-**Pen** (CCl $_4$ , 3.8 M, 73  $\mu$ m path length) with the predicted (population weighted) VCD spectrum for (*R*)-**Pen** (B3LYP/6-31G\*). (b) Comparison of experimental VCD ( $\Delta\epsilon$ ) spectrum of (*R*)-(-)-**Hex** (CCl $_4$ , 3.5 M, 73  $\mu$ m path length) with the predicted (population weighted) VCD spectrum for (*R*)-**Hex** (B3LYP/6-31G\*).

(*g* $^-$ *G* $^-$ *G* $^+$ *G* $^-$ ). Both predicted (population weighted) VCD bands of (*R*)-**Pen** (28 conformations) and (*R*)-**Hex** (82 conformations) correspond well to those observed (Figure 3). The most stable conformations are also all-*trans* conformations: (tTT) for (*R*)-**Pen** and (tTTT) for (*R*)-**Hex**. The Boltzmann populations are 22.1% for (*R*)-**Pen** and 16.0% for (*R*)-**Hex**, respectively.

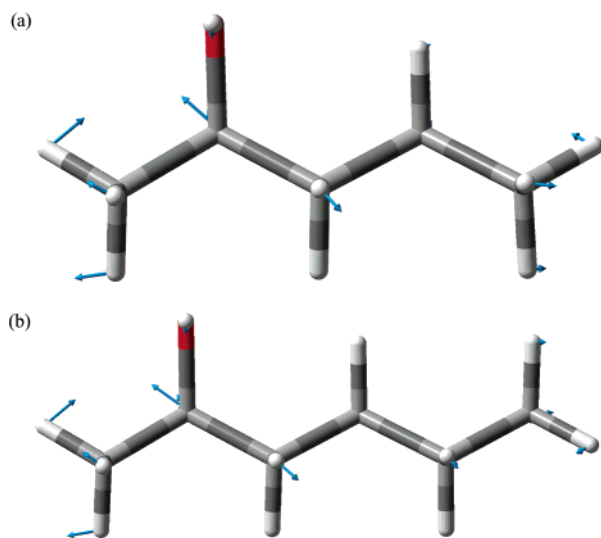
The predicted (population weighted) VCD bands of (*R*)-**Hex** (12 energetically preferable conformations, total population: 70.5%) also correspond well to those observed (Figure 4). The predicted VCD bands from the conformations (tTTT) (16.0%), (*g* $^-$ tTT) (8.5%), (tTG $^-$ T) (4.5%), (*g* $^+$ tG $^-$ T) (4.3%), and (tTTG $^-$ ) (3.7%) contribute to the population-weighted VCD band of (*R*)-**Hex** at 1148 cm $^{-1}$ .<sup>15,18</sup> No large negative contribu-

**Figure 4.** (a) Comparison of experimental VCD ( $\Delta\epsilon$ ) spectrum of (*R*)-(-)-**Hex** (CCl $_4$ , 3.5 M, 73  $\mu$ m path length) with the predicted (population weighted) VCD spectrum of 12 energetically preferable conformations for (*R*)-**Hex** (total population: 70.5%, B3LYP/6-31G\*). (b) Comparison of experimental VCD ( $\Delta\epsilon$ ) spectrum of (*R*)-(-)-**Hep** (CCl $_4$ , 3.2 M, 73  $\mu$ m path length) with the predicted (population weighted) VCD spectrum of 12 selected conformations for (*R*)-**Hep** (B3LYP/6-31G\*). (c) Comparison of experimental VCD ( $\Delta\epsilon$ ) spectrum of (*R*)-(-)-**Oct** (CCl $_4$ , 2.9 M, 73  $\mu$ m path length) with the predicted (population weighted) VCD spectrum of 12 selected conformations for (*R*)-**Oct** (B3LYP/6-31G\*).

tions from the other conformations (*g* $^+$ tTTT) (12.8%), (tG $^+$ tTT) (4.5%), (*g* $^-$ *G* $^+$ tTT) (3.9%), (*g* $^+$ *G* $^+$ tTT) (3.8%), (*g* $^+$ tTG $^-$ ) (3.1%), (tTTG $^+$ ) (3.0%), and (*g* $^+$ tTG $^+$ ) (2.4%) are found.<sup>15</sup> To compare with the other alcohols, the vibrational calculations of the corresponding 12 selected conformations for (*R*)-**Hep** and (*R*)-

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**Figure 5.** (a) Displacement vectors of a VCD band at  $1151\text{ cm}^{-1}$  for conformation (tTT) [(*R*)-Pen, B3LYP/6-31G\*]. (b) Displacement vectors of a VCD band at  $1150\text{ cm}^{-1}$  for conformation (tTTT) [(*R*)-Hex, B3LYP/6-31G\*].

**Oct** were performed.<sup>15</sup> The predicted (population weighted) VCD bands of (*R*)-Hex (total population: 70.5%) resemble those of (*R*)-Oct but not those of (*R*)-Hep (Figure 4). Each predicted VCD band near  $1148\text{ cm}^{-1}$  from the conformations (tTTT) (16.0%), ( $g^-$ -TTT) (8.5%), (tTG<sup>-</sup>T) (4.5%), ( $g^+$ TG<sup>-</sup>T) (4.3%), and (tTTG<sup>-</sup>) (3.7%) for (*R*)-Hex also resembles each from the corresponding conformations for (*R*)-Oct but not for (*R*)-Hep.<sup>15</sup> The stabilities of the corresponding conformations for (*R*)-Hex, (*R*)-Hep, and (*R*)-Oct are relatively similar to each other.<sup>15</sup> Furthermore, the vibrational calculations of all-*trans* conformations for (*R*)-CH<sub>3</sub>CHOHC<sub>*n*</sub>H<sub>2*n*+1</sub> ( $n = 2-8$ ; B3LYP/6-31G\*) were performed. Figure 1b demonstrates the predicted VCD spectra of *S*-forms. The VCD bands at  $1150\text{ cm}^{-1}$  indicate an odd–even effect and correspond well to the observed results. At  $1081\text{ cm}^{-1}$  for (*S*)-Hex, an odd–even effect with stronger intensities is also predicted. These findings with the above population results suggest that many VCD bands derived from various conformations overlap in this region, and the net observed VCD intensities are weakened. However, the VCD bands near  $1150\text{ cm}^{-1}$  lie on the edge of these absorptions, and the influence of all-*trans* conformations is relatively observed without interference.<sup>15</sup> Figure 5 shows the displacement vectors of the VCD bands for conformations (tTT) and (tTTT) [ $1151\text{ cm}^{-1}$  for (*R*)-Pen and  $1150\text{ cm}^{-1}$  for (*R*)-Hex]. The motions of the hydroxyl groups for the VCD bands near  $1150\text{ cm}^{-1}$  are very small. The main difference in the vectors between even and odd alkyl chains is associated with the motions of the terminal methyl groups in the alkyl chains with respect to those motions near the chiral center. The positions and vibrational motions of these methyl groups change in an alternating way with the number of alkyl carbon atoms with respect to the position and vibrational motions near the chiral center in the all-*trans* conformations, and at least this factor results in the odd–even effect of the predicted VCD bands for all-*trans* conformations. The conformations ( $g^-$ -TTT), (tTG<sup>-</sup>T), ( $g^+$ TG<sup>-</sup>T), and (tTTG<sup>-</sup>) for (*R*)-Hex also have a similar relationship on the displacement vectors with the corresponding conformations for (*R*)-Hep and (*R*)-Oct.<sup>15</sup> Both the motions of the terminal methyl groups in the alkyl chains and those of the substituents

near the chiral centers are necessary for the observation of the odd–even effect in the VCD bands. It is suggested that the *trans* conformations [(XTT); X = identical conformations] make the displacement vectors of the terminal methyl groups in the alkyl chains parallel between (XTT) and (X) for (*R*)-But, (*R*)-Hex, (*R*)-Oct, and (*R*)-Dec, and each VCD band near  $1150\text{ cm}^{-1}$  from the corresponding stable conformations (XTT) and (X) resembles each other. The stabilities of the corresponding conformations are also relatively similar to each other. The averaged VCD bands near  $1150\text{ cm}^{-1}$  show the clear odd–even effect without large negative contributions. The predicted VCD band of conformation (tTTT) at  $1081\text{ cm}^{-1}$  for (*R*)-Hex is assigned as C\*–O stretching, C\*–O–H bending, and O–C\*–H bending.<sup>15</sup> The intermolecular hydrogen bonding strongly shifts the VCD band at  $1081\text{ cm}^{-1}$  to higher frequencies due to the changes in force constants,<sup>16</sup> and the VCD band at  $1081\text{ cm}^{-1}$  receives large negative contributions from the VCD band at  $1118\text{ cm}^{-1}$ .<sup>15</sup> The averaged VCD bands near  $1080\text{ cm}^{-1}$  for (*R*)-Hex also overlap with the averaged VCD bands near  $1120\text{ cm}^{-1}$  (Figure 4), and the net observed VCD intensities are weakened. Ultimately, this odd–even effect of the VCD bands in solution state is ascribed to the repeated zigzag structures of the *trans* conformations. The accompanying unpolarized infrared absorption, which lacks the stereosensitivity of VCD, does not clearly show an odd–even effect in either the experimental spectra or the corresponding calculated spectra.<sup>15</sup>

## Conclusion

The odd–even effect in the solution state has been observed spectroscopically for the first time. VCD spectroscopy is currently the only technique with sufficient long-range sensitivity and stereosensitivity to hydrocarbon structure to observe the odd–even effect in solution because electronic CD lacks the necessary chromophores to detect hydrocarbon stereochemistry. From the results of solid-state analysis, it is known that odd–even effects of alkyl chains are strongly affected by all-*trans* conformations. To observe the odd–even effect in solution state, it is found that enhanced population of *trans* conformations in solution is essential. The conformational sensitivity of VCD for the chiral alcohols in solution state would be especially important for the molecular design of liquid crystals and bioactive substances such as Annonaceous acetogenins with high antitumor activities. The observations of odd–even effects in solution using VCD raise the prospect for applications using the odd–even effect in solution based on long-range chiral interactions. Application of VCD to study further the odd–even effect of alkyl chains and its structure–activity relationship study for ligand design is now in progress.<sup>13c</sup>

## Experimental Section

**Measurements.** All reagents were of commercial grade. The infrared and VCD spectra were recorded on a commercial Fourier transform VCD spectrometer, Chiralir. The VCD spectra were recorded with a 4 h data collection time at  $4\text{ cm}^{-1}$  resolution. The CCl<sub>4</sub> solutions were placed in a 73 or 498  $\mu\text{m}$  path length cell with BaF<sub>2</sub> windows. The aqueous solutions or neat liquids were placed in a 5.6  $\mu\text{m}$  path length cell with CaF<sub>2</sub> windows. In the VCD spectra presented, the raw VCD spectra of the solvents were subtracted.

**Calculations.** All geometry optimizations, conformer searches, vibrational frequencies, and absorption and VCD intensities for (*R*)-



$\text{CH}_3\text{CHOHC}_n\text{H}_{2n+1}$  ( $n = 2-8$ ) were calculated using the Gaussian 98 program<sup>17</sup> on a Pentium 4 (2.8 GHz) PC. Density functional theory with the 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  $6\text{ cm}^{-1}$  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:** Relative Gibbs free energies and populations for conformations of (*R*)-**Pen**, (*R*)-**Hex**, (*R*)-**Hep**, and (*R*)-**Oct**; observed and calculated IR spectra of (*S*)- $\text{CH}_3\text{CHOHC}_n\text{H}_{2n+1}$  ( $n = 2-8$ ); VCD spectra of (*S*)-**Pen**, (*S*)-**Hex**, and (*S*)-**Oct** in  $\text{CCl}_4$  solution at different concentrations; VCD spectra of (*S*)-**But** in aqueous and  $\text{CCl}_4$  solutions; IR spectra of (*S*)-**Oct** at different concentrations; predicted VCD and IR spectra of selected conformations for (*R*)-**Hex**, (*R*)-**Hep**, and (*R*)-**Oct**; displacement vectors of VCD bands for conformations (tTG<sup>-</sup>T), (tTG<sup>-</sup>TT), and (tTG<sup>-</sup>TTT). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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