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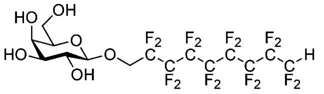
Conformational Analysis of Chiral Helical Perfluoroalkyl Chains by VCD

Kenji Monde,*,† Nobuaki Miura,† Mai Hashimoto,† Tohru Taniguchi,† and Tamotsu Inabe‡
Division of Biological Sciences, Graduate School of Science, Frontier Research Center for Post-Genomic Science and Technology, Hokkaido University, Kita-ku, Sapporo 001-0021, Japan, and Division of Chemistry, Graduate School of Science, Hokkaido University, Kita-ku, Sapporo 060-0810, Japan

Received January 11, 2006; E-mail: kmonde@glyco.sci.hokudai.ac.jp

Conventionally, perfluoroalkane has been frequently used in the polymer represented as poly(tetrafluoroethylene) (PTFE), although recently, perfluoroalkane has been utilized in a variety of research fields, such as organic synthesis.[1] Highly fluoro-substituted molecules or fragments display an affinity for fluorous media and are soluble in perfluoroalkane solvents, such as perfluoromethyl cyclohexane. To utilize this selective solubility, environmentally friendly methodologies for liquid organic synthesis are being developed as the fluorous chemistry.[1] Perfluorinated carbon chains are known to adopt a helical structure due to electrosteric repulsion of fluorine atoms in the relative 1,3-positions of the crystalline state, which was first demonstrated by Bunn and Howells using X-ray crystallography.[2] It has also been hypothesized that perfluorinated carbon chains adopt a helical structure in solution, while linear hydrocarbons have a zigzag conformation. In 1992, Hatada et al. observed conformational asymmetry of a linear perfluoroalkyl chain in optically active compounds by using ^{19}F NMR,[3] which suggested the possible helical conformation of perfluoroalkyl chains in solution. However, no other experimental evidence for the helical structure in solution has been reported. In this communication, we report the synthesis of biased helical perfluorinated side chains by the addition of chiral headgroups and observe helical structures in solution by vibrational circular dichroism (VCD). In particular, the VCD technique successfully revealed the absolute configuration of the biased simple helix in solution with the aid of theoretical calculations.[4]



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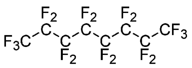

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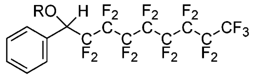

2: R = H
3: R = Bz

Chiral compounds possessing a chiral headgroup and a perfluorinated chain were synthesized via standard methods. With the goal of supramolecule construction, a fluorinated artificial glycolipid (**1**) was synthesized by direct glycosidation with a peracetyl β-D-galactopyranose and a 1*H*,1*H*,9*H*-hexadecafluoro-1-nonanol with catalysis of boron trifluoride following deacetylation.[5] To simplify its theoretical VCD calculation, a model compound, 1-perfluorooctyl-1-phenylmethanol (**2**),[5,6] was also prepared from a perfluorooctyl iodide and a benzaldehyde according to the previously described method.[3,6] The resulting racemic perfluorinated alcohol was successfully resolved optically to each enantiomer, (−)-**2** ($[\alpha]_D^{25} = -13.2$) and (+)-**2** ($[\alpha]_D^{25} = +13.3$), by the chiral HPLC system on a CHIRALCEL OD column. To elucidate their absolute configurations, the enantiomers, (−)-**2** and (+)-**2**, were transformed into the corresponding benzoate esters (+)-**3** and (−)-**3**, respectively. Their CD spectra indicate their absolute configurations as *R* for (+)-**3** and *S* for (−)-**3** by comparison to the previously reported method.[7] On the basis of these results, the absolute configuration of the first eluted enantiomer (−)-**2** was assigned as *R*, while the configuration of the second eluted one (+)-**2** was assigned as *S*.

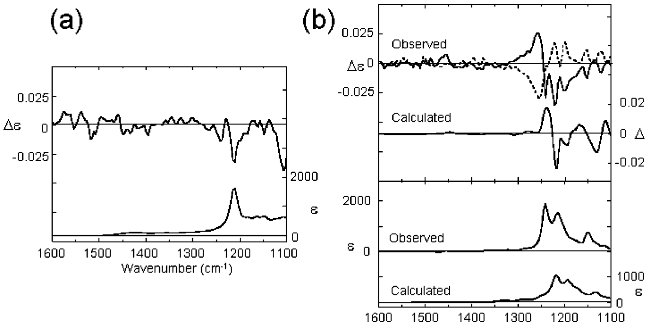

Figure 1. (a) IR (lower frame) and VCD (upper frame) spectra ($c = 0.04$ M, $l = 71$ μm) of the perfluorinated glycolipid (**1**) in DMSO-d_6. (b) Comparison of IR (lower frame) and VCD (upper frame) spectra observed (CDCl$_3$, $c = 0.06$ M, $l = 100$ μm) for (*R*)-(−)-**2** (solid line) and (*S*)-(+)-**2** (dotted line) with one calculated for (*R*)-**2**. The peak around 1240 cm^{-1} could be an artifact of complicated interpretation.

VCD measures the differential absorption of left versus right circularly polarized IR radiation by molecular vibrational transition.[8] Due to the recent availability of commercial equipment, various fields of research have begun investigating biomacromolecules as well as determining their absolute configurations with the aid of theoretical calculations.[9] Figure 1a shows the IR and VCD spectra of the fluorous glycolipid (**1**). Its IR spectrum shows the extremely strong ($\epsilon = 1600$) C−F stretch absorption[10] around 1210 cm^{-1} and the relatively weak absorption contributed by its sugar part.[11] The VCD spectrum corresponding to the C−F stretch contains a moderately negative peak, suggesting the chiral environment around the fluorine and carbon atoms. The VCD spectra of enantiomers (*R*)-(−)-**2** and (*S*)-(+)-**2** demonstrate a mirror image couplet pattern for the characteristic C−F absorption peaks at ~1250 cm^{-1}, while their IR spectra were almost identical, showing strong C−F stretch absorption ($\nu(\epsilon) = 1240$ (1900), 1220 (1500) cm^{-1}, Figure 1b). These observations clearly indicate that the VCD signals around 1200 cm^{-1} could be attributed to their helical structures. Moreover, the ^{1}H NMR signal of the benzyl proton has two different H−F coupling constants[12] ($^3J_{HF} = 17.7$ and 5.7 Hz), demonstrating that the two fluorine atoms attached to the carbon next to the benzyl carbon are in different environments with a relatively rigid conformation. To elucidate the absolute configuration of the helix and confirm the helical structure in solution, an ab initio theoretical calculation was performed.

VCD has an advantage in its sensitivity for chiral conformations, and VCD spectra can be reliably calculated using methods available in the Gaussian program. To utilize this advantage, conformational

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† Division of Biological Sciences.
‡ Division of Chemistry.

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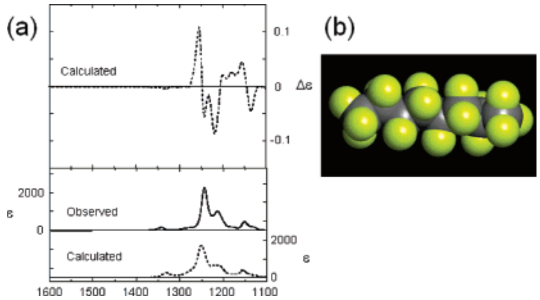

Figure 2. (a) Comparison of IR (lower frame) spectra for observed (solid line, CCl_4) and calculated (dotted line) C_8F_{18} (**4**), and a calculated virtual VCD (upper frame) spectrum for an artificial right-handed helical **4**. (b) The most stable *P* (right-handed) helical conformer of **4**.

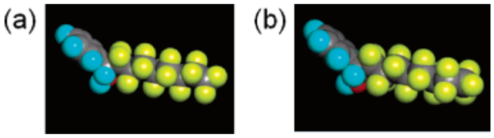

Figure 3. (a) The crystal structure of (*R*)-(−)-**2** represented by the spacefill display mode. (b) The calculated most stable conformer of (*R*)-**2**.

analysis of the simplest linear perfluoroalkane C_8F_{18} (**4**) was performed first. Theoretical calculations of perfluoroalkane or its derivatives have been occasionally examined due to their unique helical structures.[13] In this study, we utilized the quantum mechanical ab initio methods with density functional theory (DFT) calculations to obtain accurate results.

Using molecular mechanics (MM) with an MMFF94S force field from the CONFLEX program,[14] conformational analysis of the linear perfluoroalkane C_8F_{18} (**4**) was conducted. The four low-lying conformers were selected such that the cumulative Boltzmann weighted population sum was over 95%. From the conformers, the right- and left-handed helical geometries were generated such that all dihedral angles C−C−C−C were 162 or −162° since the optimized structures were not helical at the MM level. To obtain accurate energies and IR and VCD spectra, geometrical optimizations and harmonic frequency analyses were performed using DFT calculations at the B3PW91/6-31G (d,p) level of theory. For a calculated VCD spectrum of an artificial right-handed helical structure, the most stable linear right-handed structure was selected (Figure 2b).[5] Observed and calculated IR spectra were in excellent agreement with each other, demonstrating an accurate calculation. Additionally, the virtual VCD spectrum showed a strong positive peak around 1250 cm^{-1} for the right-handed helical structure (Figure 2a).

The (*R*)-1-perfluorooctyl-1-phenylmethanol (**2**) was also submitted to the ab initio calculation in a similar manner.[5] Though relative energies of the selected low-lying 12 conformers were rather close, the only differences among these conformers were a direction of the hydroxyl group and a rotation angle between the benzylic chiral carbon and the neighboring CF_2 carbon. Averaged IR and VCD spectra were calculated with the Boltzmann weighted populations for the low-lying 12 conformers. Figure 1b shows the observed and calculated spectra of **2**. As in the linear perfluoroalkane **4**, its helicity for the first eluted enantiomer (*R*)-(−)-**2** was found to be *P* (right-handed) by direct comparison with the C−F stretch band.

To confirm the results from the VCD investigation, an X-ray diffraction study of (*R*)-(−)-**2** was conducted. Figure 3a shows a crystal structure of (*R*)-(−)-**2** indicating the right-handed (*P*) helical structure of at least five CF_2 groups from the chiral headgroup in the perfluoroalkyl side chain of **2**.[5] The crystal structure of (*R*)-(−)-**2** was comparable to that of the most stable conformer of (*R*)-**2** calculated above (Figure 3b). This result agreed well with the predicted biased structure and the right-handed helical structure in solution by the VCD study. However, the helical structure in the solid state was broken at the end part of the perfluoroalkyl side chain, possibly due to packing effects in crystals, especially due to the tightly fixed molecular arrangement of strong intermolecular O−H···O hydrogen bonds between the neighboring hydroxyl groups (O···O distance = 2.787(6) Å).

In conclusion, we have succeeded in controlling the biased helicity of perfluoroalkyl chains by the simple addition of a chiral headgroup. In addition, for the first time, we determined its helicity by utilizing the C−F characteristic VCD band with the aid of an ab initio calculation, which was supported by an X-ray crystallographic study. The C−F VCD band shows promise to be a good marker for the verification of C−F helicity in future chiral perfluoroalkane studies. Many scientists have generated magnificent synthetic helical assemblies,[15] but to the best of our knowledge, this is the most basic chiral helix. Perfluorinated and semifluorinated compounds have been widely used in the formation of superstructures, such as micelles and self-assembled monolayers. This VCD study could also be found to be applicable to helical supramolecular chemistry.

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Supporting Information Available: Experimental procedures, spectra data for new compounds, VCD spectra, and computation (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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