Tetrahedron Letters 50 (2009) 1689–1692

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Vibrational CD spectroscopy as a powerful tool for stereochemical study of cyclophynes in solution

De Lie An [a,*], Qiang Chen [a], Jingkun Fang [a], Hong Yan [a], Akihiro Orita [b], Nobuaki Miura [c], Atsufumi Nakahashi [c], Kenji Monde [c,*], Junzo Otera [b,*]

[a] State Key Laboratory of Chemo/Biosensing and Chemometrics, Department of Chemistry, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China
[b] Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama 700-0005, Japan
[c] Division of Biological Sciences, Graduate School of Science, Frontier Research Center for Post-Genome Science and Technology, Hokkaido University, Kita-ku, Sapporo 001-0021, Japan

ARTICLE INFO

Article history:
Received 9 December 2008
Revised 15 January 2009
Accepted 16 January 2009
Available online 23 January 2009

Keywords:
Aromatic compound
Chirality
Cycloalkyne
VCD
IR

ABSTRACT

Stereochemical study of cyclophynes, which is otherwise rather difficult to perform, can be achieved by vibrational CD spectroscopy.

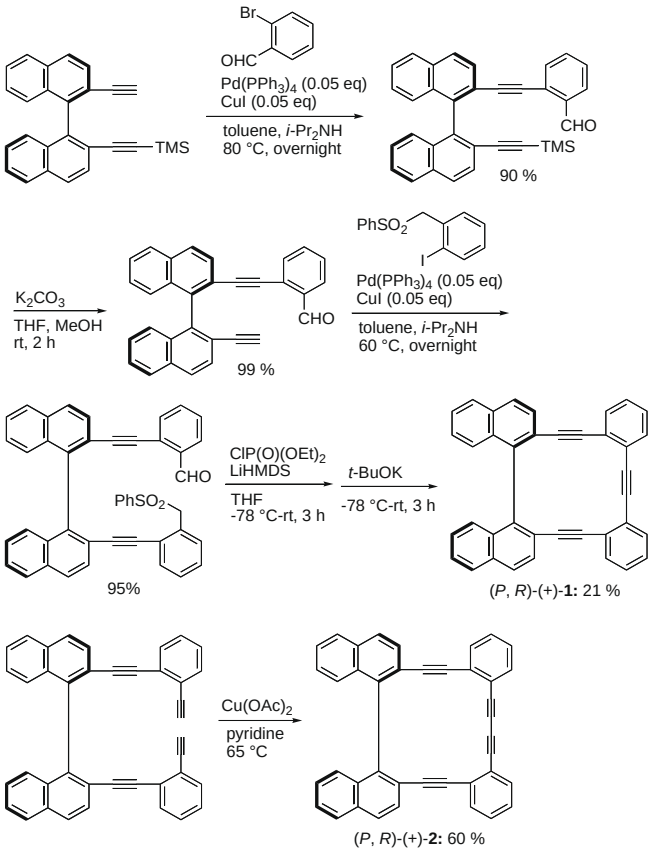
The cyclophyne chemistry has met with great progress for the last decade due to increasing attention to their unique cyclic arylene ethynylene architectures.[1] Two- or three-dimensional structures are the focus of interest in view of conformational features and electronic states. However, the conformational study, particularly in solution, remains almost unexplored, since most of cyclophynes are hydrocarbons, lacking functional groups from which to acquire structural information by means of common spectroscopic methods such as NMR. We previously suggested that molecular chirality could provide a clue to probe conformational features of three-dimensional cyclophynes in solution.[2] Electronic circular dichroism (ECD) was invoked for this purpose. Unfortunately, however, the difficulty in simulating ECD spectra by theoretical calculations involving excited electronic states failed to give precise stereochemical information with full reliability. In contrast, vibrational circular dichroism (VCD), in principle, can show better matching between experimental and theoretical outcomes, because calculations of vibrational spectra are feasible on the basis of the ground electronic state only.[3] Importantly, molecules should be conformationally rigid to a considerable degree to attain reliable theoretical estimation. Bearing these issues in mind, we postulated that the VCD method would serve suitably for configurational as well as conformational elucidation of shape-persistent cyclophynes. This is indeed the case, as disclosed herein.

We synthesized conformationally rigid enantiopure cyclophynes, (*R, P*)-(+)-**1** and (*R, P*)-(+)-**2**, according to the procedures shown in Scheme 1.[4] A precursor with terminal formyl and benzyl sulfonyl functionalities was subjected to intramolecular double elimination reaction[5] to furnish (*R, P*)-**1**, while intramolecular Eglington coupling[6] of a precursor with two terminal acetylenes afforded (*R, P*)-**2** in reasonable yield. The corresponding *S* enantiomers were prepared in the same way.

Figures 1a, c and e, g demonstrate VCD and IR spectra of (*R*)- and (*S*)-**1** and **2**, respectively, measured in $CDCl_3$.[7] A pair of enantiomers exhibited completely antipodal profiles in VCD spectra. Significantly, these spectra are almost superimposed on the spectra calculated on the basis of molecular mechanics and ab initio density functional theory at B3PW91/6-31G(d) level (Figs. 1b, d and f, h), confirming the reliability of the absolute configurations and optimized conformations obtained by calculations (Figs. 2a and b).[8] It follows therefore that these non-polar molecules possess nearly the same conformations in solution and gas phase, respectively, since they are free from significant intermolecular interactions and solvation. Utility of the VCD method for stereochemical elucidation of the cyclophynes was highlighted by comparison with acyclic analogue (*R*)-**3**,[9] which also gave excellent consistency between experimental and calculated spectra (Figs. 1i–l). The opti-

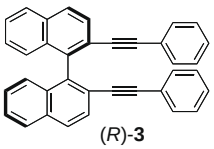
* Corresponding authors. Tel./fax: +86 731 882 7944 (D.L.A.), tel.: +81 86 256 9525; fax: +81 86 256 4292 (J.O.), tel./fax: +81 11 706 9042 (K.M.)
E-mail addresses: deliean@sina.com (D.L. An), kmonde@glyco.sci.hokudai.ac.jp (K. Monde), otera@high.ous.ac.jp (J. Otera).

0040-4039/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.01.095



Scheme 1. Synthesis of (*P*,*R*)-(+)-**1** and (*P*,*R*)-(+)-**2**.

mized conformation of this acyclic compound (Fig. 2c)[8] differs distinctly from those of **1** and **2**. The naphthyl planes are almost coplanar with the benzene rings of the phenylethynyl moieties in **3**, whereas connection of the benzene rings through a yne or diyne unit in **1** and **2** induces rotation of the dihedral angle between the naphthyl and benzene rings nearly to 90°. Analysis of vibrational modes reveals that **3** exhibits characteristic absorption bands that are assignable to C–H bending modes in the binaphthyl groups in addition to weak bands that are assignable to C–H bendings in the phenyl groups except for one at 1357 cm^{-1} arising from coupled C–H bendings in both groups.[10] Interestingly, **1, 2**, and **3** show common split typed VCD bands around 1519 and 1512 cm^{-1} derived from their biphenyl group, which are potentially characteristic markers arising from their absolute configuration. As the structural differentiation between **1** and **2**, the compound **1** shows a band derived from C–H bending in the phenyl or phenylene group at 1491 cm^{-1}, while other VCD signals of **1** and **2** are generally similar. Apparently, the cyclophyne formation facilitates vibrational couplings of the C-H bending modes in the binaphthyl and phenylene groups.



(*R*)-**3**

The success of single crystal X-ray analysis of (*S, M*)-(−)-**2** (Fig. 3)[11] allowed us to compare the conformations in the solution and crystalline states. Heats of formation were calculated to be −7811.2 kcal/mol and −7522.3 kcal/mol for the conformations shown in Figures 2b and 3, respectively.[10] The conformation, though being C_2-symmetric in solution, deviates from the C_2 symmetry substantially in the crystal. This is most clearly reflected on the dihedral angles between the planes of the *o*-phenylene and naphthalene rings: one is 78.8° (C_{19}–C_{20}–C_{23}–C_{24}) and the other is 86.1° (C_2–C_1–C_{38}–C_{37}) in the crystal in sharp contrast to 84.5° for both dihedral angles in solution. Such distortion gives rise to the less favorable heat of formation in the crystal than in solution ($\Delta\Delta H$ = 288.9 kcal/mol), which is presumably compensated by crystal packing energy.

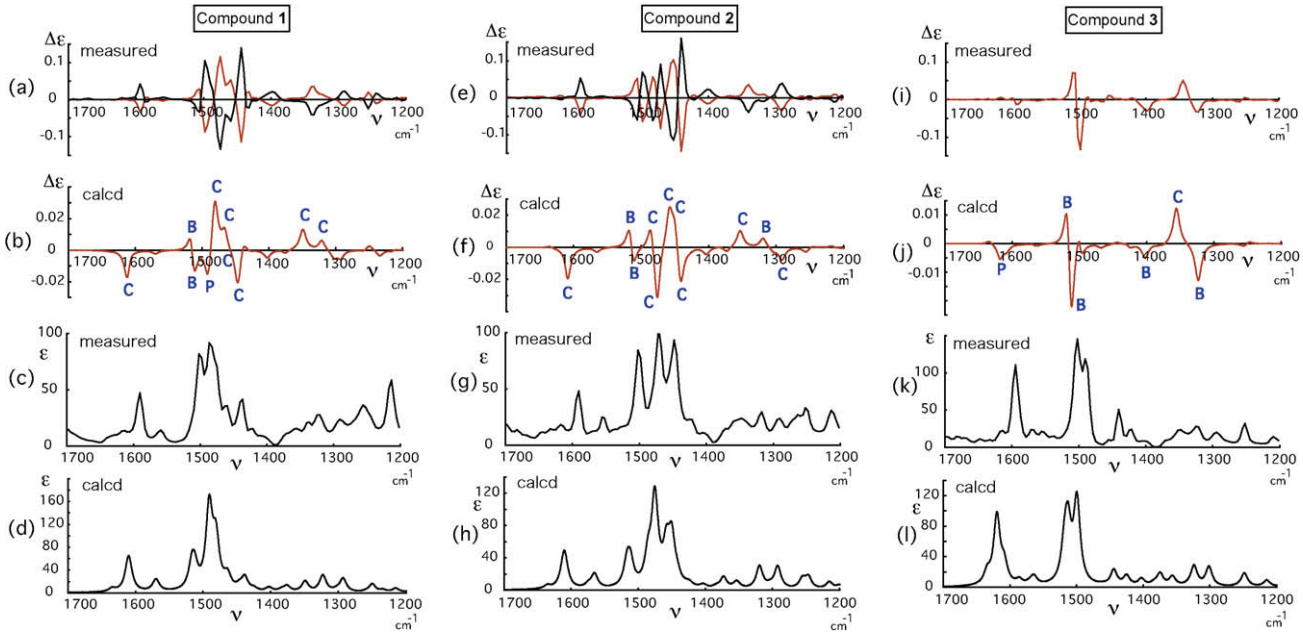


Figure 1. Measured and calculated VCD and IR spectra (red line for *R* enantiomers and black line for *S* enantiomers). VCD: **1** (a), (b); **2** (e), (f); **3** (i), (j). IR: **1** (c), (d); **2** (g), (h); **3** (k), (l). Assignment: B for C-H bending in the binaphthyl group; P for C–H bending in the phenyl or phenylene group; C for coupled C–H bending.

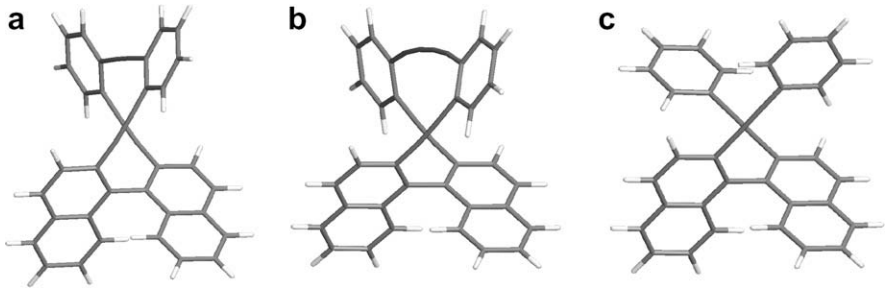


Figure 2. Optimized conformations. (a) **1**, (b) **2**, and (c) **3**.

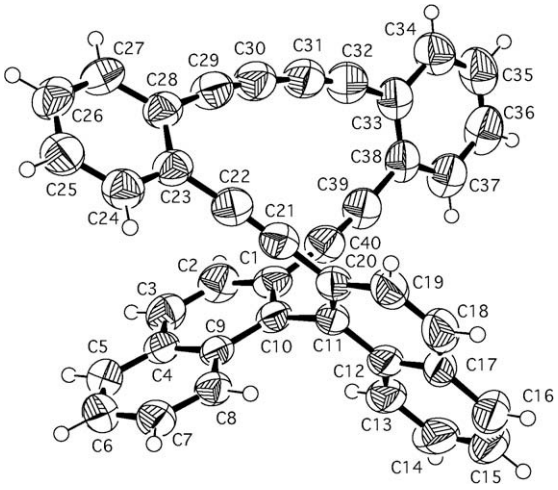


Figure 3. ORTEP drawing of crystal structure of (*S, M*)-(−)-**2**. Thermal ellipsoids are set at the 50% probability level (at 293 K). Selected bond lengths [Å] and angles [°]: C21–C22 1.200, C28–C29 1.422, C29–C30 1.198, C30–31 1.364, C20–C21–C22 173.8, C21–C22–C23 176.2, C28–C29–C30 176.3, C29–C30–C31 174.7, C19–C20–C23–C24 78.8, C2–C1–C38–C37 86.1, C1–C10–C11–C20 107.2.

In summary, VCD has proved to be useful for analyses of absolute configurations and conformations of shape-persistent chiral cyclophynes in solution, which is otherwise rather difficult to perform. Notably, lack of intermolecular interactions of non-polar hydrocarbon molecules results in excellent consistency between the conformations measured in solution and calculated in the gas phase. Conformational profiles of cyclophynes can be delineated well by comparison with an acyclic counterpart. Through combination with X-ray analysis, the conformational differences in solution and crystal can also be revealed. As such, VCD will be of great use for cyclophane chemistry.

Acknowledgements

We thank Professor S.-I. Nishimura at Hokkaido University for his valuable suggestions. This work was supported by the National Natural Science Foundation of China (Grant Nos. 20272012 and 20672033), Hunan Provincial Natural Science Foundation of China (No. 07JJ3026), and the Grant-in-Aid for Scientific Research (Nos. 16656023, 20651055 and 20310127) from MEXT, Japan. A. N. gratefully acknowledges a fellowship from the Japan Society of the Promotion of Science.

Supplementary data

Full synthetic details for the preparation of **1** and **2**, characterization of their physical properties and calculations of vibrational modes as well as heat of formation are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.095.

References and notes

1. Tobe, Y.; Sonoda, M. In *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, Germany, 2004. Chapter 1, p 1; (b) Höger, S. In *Acetylene Chemistry*; Diederich, F., Stang, P. J., Tykwinsky, R. R., Eds.; Wiley-VCH: Weinheim, Germany, 2005. Chapter 10, p 427.
2. An, D.-L.; Zhang, Y.-J.; Chen, Q.; Zhao, W.-Y.; Yan, H.; Orita, A.; Otera, J. *Chem. Asain J.* **2007**, *2*, 1299.
3. (a) Keiderling, T. A. In *Circular Dichroism: Principles and Applications*; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000; p 621; (b) Freedman, T. B.; Cao, X.; Dukor, R. K.; Nafie, L. A. *Chirality* **2003**, *15*, 743; (c) Polavarapu, P. L.; He, J. *Anal. Chem.* **2004**, *76*, 61A; (d) Taniguchi, T.; Miura, N.; Nishimura, S.-I.; Monde, K. *Mol. Nutr. Food Res.* **2004**, *48*, 246; (e) Nafie, L. A.; Dukor, R. K. In *Chiral Analysis*; Busch, K. W., Busch, M. A., Eds.; Elsevier: Amsterdam, 2006. p 505; (f) Taniguchi, T.; Monde, K. *Trends Glycosci. Glycotechnol.* **2007**, *19*, 149; (g) Kellenbach, E. R.; Dukor, R. K.; Nafie, L. A. *Spectrosc. Eur.* **2007**, *19*, 15; (h) Polavarapu, P. L. *Chem. Rec.* **2007**, *7*, 125; (i) Stephens, P. J.; Devlin, F. J.; Pan, J.-J. *Chirality* **2008**, *20*, 643.
4. *Synthesis of* ***1***: To a round-bottomed flask were added (*R*)-2-(2-formylphenylethynyl)-2′-(2-(phenylsulfonylmethyl)phenylethynyl)-1,1′-binaphthalene (127 mg, 0.2 mmol), diethyl chlorophosphate (34 mg, 0.2 mmol), and THF (100 mL) under nitrogen. To the solution was added LiHMDS (0.22 mL, 1.0 M, 0.22 mmol) at −78 °C. After the mixture had been stirred at rt for 3 h, a suspension of *t*-BuOK (224 mg, 2.0 mmol) in THF (10 mL) was added at −78 °C. After the mixture had been stirred at rt for 3 h, the reaction mixture was poured into aqueous NH_4Cl. After extraction with CH_2Cl_2, the combined organic layer was dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 4:1) to give (*R, P*)-(+)-**1** as colorless crystals (20 mg, 21.0% yield). Compound **1**: mp 183–185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, J = 8.5 Hz, 2H), 7.15 (t, J = 8.5 Hz, 2H), 7.21–7.27 (m, 6H), 7.44–7.50 (m, 4H), 7.72 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 90.85 (2C), 92.05 (2C), 92.94 (2C), 121.87 (2C), 126.30 (2C), 126.36 (2C), 126.41 (2C), 126.50 (2C), 126.85 (2C), 127.80 (2C), 127.88 (2C), 128.00 (2C), 128.21 (2C), 129.60 (2C), 131.12 (2C), 131.28 (2C), 132.69 (2C), 132.93 (2C), 137.85 (2C); (*R, P*)-(+)-**1**: $[\alpha]_D^{16.9}$ 241.5 (*c* 0.019, $CHCl_3$), (*S, M*)-(−)-**1**: $[\alpha]_D^{25.9}$ -242.8 (*c* 0.019, $CHCl_3$); MALDI-TOF MS: *m/z* calcd for $C_{38}H_{20}$ (M^+): 476.5654; found 476.1571.*Synthesis of* ***2***: To a 100 mL of flask were added $Cu(OAc)_2$ (6.5 mg, 0.028 mol) and pyridine (65 mL). To the suspension was added (*R*)-2,2′-bis(2-ethynylphenylethynyl)-1,1′-binaphthalene (182 mg, 0.36 mmol) in pyridine (10 mL) at 60 °C over 4 h by syringe pump, and the mixture was stirred at 60 °C for 2 h. After evaporation, the crude product was poured into NH_4Cl aq and extracted with CH_2Cl_2. After the combined organic layer had been dried over $MgSO_4$ and evaporated, the residue was subjected to column chromatography on silica gel (hexane/CH_2Cl_2, 3:1) to give (*R, P*)-(+)-**2** (108 mg, 60% yield). Compound **2**: mp >165.5 °C decomp.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.13 (m, 6H), 7.25–7.28 (m, 4H), 7.32 (t, J = 7.8 Hz, 2H), 7.45 (t, J = 8.0 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.83–7.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.32, 83.07, 90.26, 93.58, 121.38, 124.88, 126.37, 126.42, 126.61, 127.58, 127.87, 127.97, 128.39, 129.30, 129.72, 130.92, 132.32, 133.07, 139.12; MS (APCI): 501.2 (M^++1, 17); (*R, P*)-(+)-**2**: $[\alpha]_D^{19}$ 560.4 (*c* 5.1, $CHCl_3$), (*S, M*)-(−)-**2**: $[\alpha]_D^{19}$ −562.4 (*c* 5.8, $CHCl_3$).
5. (a) Otera, J. *Pure Appl. Chem.* **2006**, *78*, 731; (b) Orita, A.; Otera, J. *Chem. Rev.* **2006**, *106*, 5387.
6. Eglington, G.; McCrae, W. *Adv. Org. Chem.* **1963**, *4*, 225.
7. *Measurement of the VCD spectra of* ***1, 2,*** *and* ***3***: VCD spectra were measured on a Bomem/BioTools Chiralir spectrometer at a resolution of 8 cm^{-1} under an ambient temperature. All VCD spectra are the average of three blocks of 4500 scans. Samples were dissolved in $CDCl_3$ and then placed in a 100 μm CaF_2 cell (KIII 64744 JASCO). The concentrations were as follows: (*R, P*)-**1**, (*S, M*)-**1**: 0.31 M, (*R, P*)-**2**: 0.17 M, (*S, M*)-**2**: 0.19 M, and (*R*)-**3**: 0.32 M. The IR and VCD

spectra were corrected by a solvent spectrum obtained at the same experimental conditions, and presented in molar absorptivity ε (L/mol cm).

8. *Calculation of the VCD spectra of **1**, **2**, and **3***: Rough conformational analyses of compounds **1**, **2**, and **3** were carried out with CONFLEX search, which gave only one conformation for each compound. The geometries were optimized with the density functional theory (B3PW91/6-31G(d) level of theory). Harmonic vibrational analyses were carried out to obtain the frequency and the intensity of the IR and VCD spectra. To create the final spectra, the intensities of obtained line spectra were convoluted with Lorenzian bandshapes of 8 cm^{-1} width. Frequencies were scaled with a factor 0.97.
9. (a) Baidossi, W.; Schumann, H.; Blum, J. *Tetrahedron* **1996**, *52*, 8349; (b) Orita, A.; An, D.-L.; Nakano, T.; Yaruva, J.; Ma, N.; Otera, J. *Chem. Eur. J.* **2002**, *8*, 2005.
10. See Supplementary data.
11. Full crystallographic data have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC-689743.