

The Nakanishi Symposium

on Natural Products & Bioorganic Chemistry

Nihon University
March 20, 2018

Sponsored by
The Chemical Society of Japan
&
The American Chemical Society



Harada, Nobuyuki
Professor Emeritus, Tohoku University

■EDUCATION

- | | |
|---|------|
| B. Sc. Chemistry, Faculty of Science, Tohoku University | 1965 |
| Ph.D. Organic Chemistry, Tohoku University (Prof. K. Nakanishi) | 1970 |

■ACADEMIC CAREER

- | | |
|---|-----------|
| ➤ Tohoku University | 1970—2006 |
| Chem. Res. Inst. of Nonaqueous Solutions, Inst. for Chem. Reaction Science, and Inst. of Multidisciplinary Res. for Advanced Materials, Research Associate, Associate Professor, and then Professor of Chemistry. | |
| ➤ Columbia University, USA | 1973—1975 |
| Dept. of Chem., Postdoc (Prof. K. Nakanishi) | |
| ➤ Institute for Molecular Science, Okazaki Nat. Res. Inst. | 1980—1982 |
| Adjunct Associate Professor. | |

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|---|-----------|
| ➤ Du Pont de Nemours & Company, USA | 1987 |
| Experimental Station, Visiting Res. Scientist | |
| ➤ Columbia University, USA | 2006—2009 |
| Dept. of Chem., Visiting Researcher/Scholar and | |
| Senior Research Scientist (Prof. K. Nakanishi) | |

■RESEARCH TOPICS

- a) Natural Products Chemistry and Structural Organic Chemistry.
- b) Theory of Circular Dichroism, and Development of the CD Exciton Chirality Method.
- c) Enantioresolution, Absolute Configurational and Conformational Studies of Chiral Compounds by CD, NMR, and X-Ray Methods Using Novel Chiral Molecular Tools, CSDP and M α NP Acids.
- d) Molecular Machine: Light-Powered Chiral Molecular Motors.

■SELECTED PUBLICATIONS

1. A Method for Determining the Chiralities of Optically Active Glycols. N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, **91**, 3989-3991 (1969).
2. The Exciton Chirality Method and its Application to Configurational and Conformational Studies of Natural Products. N. Harada, and K. Nakanishi, *Acc. Chem. Res.*, **5**, 257-263 (1972).
3. N. Harada and K. Nakanishi, "*Circular Dichroic Spectroscopy – Exciton Coupling in Organic Stereochemistry –*", University Science Books, Mill Valley, California, and Oxford University Press, Oxford (1983).
4. The Absolute Stereochemistries of 6,15-Dihydro-6,15-ethanonaphtho[2,3-*c*]-pentaphene and Related Homologues as Determined by both Exciton Chirality and X-ray Bijvoet Methods. N. Harada, Y. Takuma, and H. Uda, *J. Am. Chem. Soc.*, **98**, 5408-5409 (1976).
5. Light-driven Monodirectional Molecular Rotor. N. Koumura, R. W. J. Zijlstra, R. A. van Delden, N. Harada, and B. L. Feringa, *Nature*, **401**, 152-155 (1999).
6. HPLC Separation of Diastereomers: Chiral Molecular Tools Useful for the Preparation of Enantiopure Compounds and Simultaneous Determination of Their Absolute Configurations. N. Harada, *Molecules*, **21**, number 1328 (2016).

AWARDS

- | | |
|--|------|
| a) Chemical Society of Japan Award for Creative Work | 1984 |
| b) Molecular Chirality Award | 2000 |
| c) Molecular Chirality Distinguished Service Award | 2015 |

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Nakanishi Symposium 2018

Organized by : Nakanishi Symposium Organizing Committee

Co-organized by: Chemical Society of Japan,

Division of Natural Products Chemistry & Biological Science

Date March 20th, 2018, 13:30-17:30

Venue Nihon University (S2; 2F 1326, 13th Bldg., Funabashi Campus)

Program

■ 13:30-14:00 Award Ceremony of Nakanishi Prize 2018

Presider Prof. Michio Murata (Osaka University)

Prize Winner of the Nakanishi Prize 2018:

Prof. Nobuyuki Harada; Professor Emeritus, Tohoku University

■ 14:00-17:00 Nakanishi Symposium

Presider Prof. Shigeru Nishiyama (Keio University)

14:00- *“Determining Molecular Configuration and Conformation by Vibrational Circular Dichroism: from Small Molecules to Macromolecules”*

Prof. Tohru Taniguchi: (Hokkaido University)

14:30- *“Porphyrin-based Chiroptical Sensors of Molecular and Supramolecular Chirality”*

Prof. Nina Berova (Columbia University)

Presider Prof. Keisuke Suzuki (Tokyo Institute of Technology)

15:00- *“In the Rising CD Era, How Can Mosher’s Method Survive?”*
Prof. Takenori Kusumi (Tokyo Institute of Technology)

15:30- *“A Challenge of Organic Synthesis to Ciguatera Fish Poisoning”*

Prof. Masahiro Hirama (Tohoku Univ. & AcroScale, Inc.)

16:00-16:10 ---Break---

Presider Prof. Michio Murata (Osaka University)

16:10- **Award Lecture**

“Chiral Molecular Science: from the Development of CD Exciton Chirality Method to the Invention of Light Powered Chiral Molecular Motors”

Prof. Nobuyuki Harada (Professor Emeritus, Tohoku Univ.)

■ 17:10- Closing Remarks

Determining Molecular Configuration and Conformation by Vibrational Circular Dichroism: from Small Molecules to Macromolecules

Tohru Taniguchi

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“CD [circular dichroism] spectroscopy is still one of the least used physical tools and causes most organic chemists headaches,” wrote Prof. Koji Nakanishi in his ACS autobiography in 1991.¹ The current status of CD is not significantly different; CD spectroscopies remain as much less used methods for structural analysis than, for example, NMR spectroscopy and mass spectrometry. However, the reliability and versatility of CD techniques have considerably improved owing to the development of vibrational circular dichroism (VCD) spectroscopy and density functional theory (DFT) calculations of ECD (electronic circular dichroism) and VCD spectra. These developments established CD spectroscopy as a tool to elucidate the configuration and conformation of small organic molecules.²

Structural determination using VCD spectroscopy is normally carried out by comparing experimental spectra and DFT-predicted ones. Although this procedure is effective for small, rigid, hydrophobic molecules, its applicability for medium-sized, flexible, and/or hydrophilic molecules is yet to be explored. Meanwhile, structural analysis based on ECD spectroscopy has been performed without theoretical calculations by using the ECD exciton chirality method developed by Profs. Harada and Nakanishi.³ Inspired by the ECD exciton chirality method, I invented a “VCD exciton chirality method”, which enables structural determination just by observing a strong bisignate VCD signal originating from interactions between two or more carbonyl groups.⁴ The development of this method partially, though not entirely, solved the drawback of the current DFT-based VCD

structural determination.

With VCD theoretical calculations and the VCD exciton chirality method in hand, I have been studying the stereostructure of various molecules including carbohydrates, lipids, peptides, nucleosides, synthetic small molecules and macromolecules. Some of these topics should demonstrate the advantages of VCD spectroscopy over other methods, such as the capability of its picosecond shutter speed for elucidating detailed molecular conformations.^{2,5}

This presentation will focus mostly on my recent VCD results on flexible lipids, molecules containing five-membered rings, and axially chiral molecules. VCD spectroscopy is not a panacea for all structural problems, but this presentation should address its usefulness for various stereostructural studies.⁶

References:

1. K. Nakanishi, *A Wandering Natural Products Chemists*, ed. by J. I. Seeman, American Chemical Society, Washington, D. C., **1991**, p. 230 (Profiles, Pathways and Dreams Series). The quote is on page 74, but I recommend reading through the entire book.
2. This paragraph is cited from the following article with some modifications: Taniguchi, T. *Bull. Chem. Soc. Jpn.* **2017**, *90*, 1005.
3. Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1969**, *91*, 3989.
4. Taniguchi, T.; Monde, K. *J. Am. Chem. Soc.* **2012**, *134*, 3695.
5. Taniguchi, T.; Nakano, K. et al. *Org. Lett.* **2017**, *19*, 404.
6. I am grateful to Prof. Kenji Monde for his generous support and encouragement. I would like to express my sincere gratitude to Prof. Koji Nakanishi (Columbia University), Prof. Nobuyuki Harada (Tohoku University), and Prof. Nina Berova (Columbia University) for providing me an opportunity to learn the ECD exciton chirality method.

Porphyrin-based Chiroptical Sensors of Molecular and Supramolecular Chirality

Nina Berova

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In the past few decades porphyrins and metalloporphyrins (P) attracted a great attention in response to the growing interest in development of more versatile and efficient sensors for determination of chirality at molecular and supramolecular level. The situation where two or more porphyrins reside in chiral environment and interact through space appears particularly beneficial for stereochemical analysis since this interaction leads to a very intense ECD response observable even on a sub-microscale level.^{1,2} Discussion will include: i) determination of AC of natural products by chemical/long-range P/P ECD exciton coupling protocol¹; ii) supramolecular analysis of AC of chiral bidentate guests by stereodifferentiative complexation to achiral dimeric metalloporphyrins receptors-hosts²; iii) complexation between chiral tweezers and achiral substrates³; iv) ECD analysis of covalent porphyrin conjugates of DNA⁴, PNA, as well as ICD analysis of non-covalent B /Z DNA-porphyrin complexes⁵.

References:

1. Pescitelli, G.; Di Bari, L.; Berova, N. *Chem. Soc. Rev.* **2011**, 4603; **2014**, 5211.
2. Berova, N.; Pescitelli, G.; Petrovic, A.; Proni, G., *Chem. Commun.* **2009**, 5958.
3. Saha, B.; Ikabal, S.; Petrovic, A.; Berova, N.; Rath, S., *Inorg. Chem.* **2017**, 3849.
4. Mammana, A.; Pescitelli, G.; Asakawa, T.; Jockusch, S.; Petrovic, A.; Monaco, R.; Purrello, R.; Turro, N. J.; Nakanishi, K.; Ellestad, G.; Balaz, M.; Berova, N., *Chem.-Eur. J.* **2009**, 15, 11853.
5. Gangemi, C.M.A.; D'Urso, A.; Tomaselli, G.A.; Berova, N.; Purrello, R., *Inorg. Biochem.* **2017**, 173, 141.

In the Rising CD Era, How Can Mosher's Method Survive?

Takenori Kusumi

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Since Professor Harry S. Mosher reported the MTPA reagent for determining the absolute configuration of secondary alcohols by NMR spectroscopy in 1973,¹ this 'Mosher's method' has been widely used by organic chemists, boosted by the rapid development of the NMR techniques which made the assignment of proton signals quite easy.

The present speaker, together with several collaborators, has developed other NMR chiral reagents similar to MTPA (and MPA) such as (1) 1NMA, 2NMA, and 2ATMA applicable to secondary alcohols, (2) PGME for carboxylic acids, and (3) sulfoximine for sulfoxides.²

These methods are empirical ones and have a minor disadvantage that one must prepare two diastereomers using R- and S-reagents, although the task may not be too troublesome for most of organic chemists.

On the other hand, CD is strictly based on theoretical physics, and more 'white color'-ish (computer-works in an air-conditioned room) compared to the above mentioned rather 'alchemy'-ish methods (handworks with the sweat on the brow).

Obviously, usefulness of CD in elucidation of the absolute configuration of natural products has been strenuously revealed by Professor Koji Nakanishi followed by his renowned collaborators, Professor Nobuyuki Harada,³ the awardee of 2018 Nakanishi Prize, and Professor Nina Berova of Columbia University, a co-editor of journal 'Chirality'.

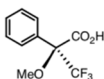
Very recently, ECD (Electronical CD)⁴ and VCD (Vibrational CD)⁵ based on TDDFT (time dependent density functional theory) have emerged as a strong tool for the absolute configuration assignment.

Owing to the impossible-to-catch-up-with advance of computer, one can use these methods on the PC level these days. The results seem to be reliable because the absolute configuration can be deduced by comparing the experimental spectrum with the calculated one on a display.

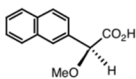
For now, it can be said that the Mosher's method could not be forgotten when one deals with the very flexible molecules, for which even the computer cannot tell the stable conformations.

References:

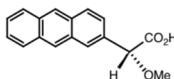
1. Dale, J. A.; Mosher, H. S., *J. Am. Chem. Soc.* **1973**, *95*, 512.
2. Kusumi, T.; Ooi, T.; Ohkubo, Y.; Yabuuchi, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 965.
3. Harada, N.; Nakanishi K. "Circular Dichroism—Application to the Stereochemistry of Organic Compounds" Tokyo Kagaku Dojin, Tokyo, **1982**.
4. Pescitelli, G.; Di Bari, L.; Berova, N., *Chem. Soc. Rev.* **2014**, 5211.
5. Taniguchi, T.; Monde, K. *J. Synth. Org. Chem. Jpn.* **2017**, *75*, 522.



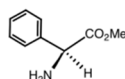
MTPA



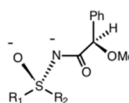
2NMA



2ATMA



PGME



Sulfoximine

A Challenge of Organic Synthesis to Ciguatera Fish Poisoning

Masahiro Hirama

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Ciguatera fish poisoning (CFP) caused by the consumption of fish that have accumulated ciguatoxins (CTXs) affects more than 50,000 people annually. The spread of CFP causes tremendous damage to public health, fishery resources, and the economies of tropical and subtropical endemic regions. The difficulty in avoiding CFP arises from the lack of sensitive and reliable analytical methods for detection and quantification of CTXs in ciguatoxic fish, along with the normal appearance, smell, and taste of fish contaminated with the causative toxins. Thus, an accurate, sensitive, routine, and portable detection method for CTXs is urgently required.

Total synthesis of ciguatoxins (CTXs) is a formidable challenge, yet is the sole realistic solution for obtaining sufficient quantities of CTXs for biological, medical, and pharmacological studies. There was little prospect for our success in the total synthesis of CTXs and furthermore, even the absolute stereochemistry of CTXs was unknown, when we launched our synthetic endeavor in 1989.

We first implicated the absolute configuration of CTX using the **Harada-Nakanishi Exciton chirality CD** method with the synthetic model compounds. Then, our 12-year effort culminated in the first total synthesis of CTX3C in 2001.¹ Our synthesis was appreciated as “The Art of Total Synthesis” by *Science* (**2001**, 294, 1842), and “Organic Chemistry Takes on Tropical Seafood Poisoning” by *The Lancet* (**2001**, 358, 1278). Our total synthesis unambiguously established the configuration of CTXs as implicated by the CD studies. Since then, our highly convergent and unified strategic approach featuring

chemoselective RCM/radical cyclization reactions as key tactics has been improved, and enabled the total synthesis of three other important Pacific congeners, 51-hydroxyCTX3C, CTX1B, and 54-deoxyCTX1B, as well as F-ring modified analogs.² The synthesis of these compounds has significantly impacted the biological and pharmacological studies of CTXs.

The second aim of our research was developing anti-ciguatoxin antibodies and antibody-based immunoassays. We therefore planned a synthesis-based approach using rationally designed synthetic haptens to address the problem of antibody development. Numerous immunization studies in collaboration with Profs. Tsumuraya and Fujii using synthetic hapten-keyhole limpet hemocyanin (KLH) conjugates showed that the polyether fragments, which possess more than five ether rings and have a surface area larger than 400Å², can be used as synthetic haptens to provide highly sensitive and specific anti-CTX monoclonal antibodies (mAbs). These mAbs (10C9, 3D11, 8H4, and 3G8) have been used to develop a direct sandwich enzyme-linked immunosorbent assay (ELISA) method for the reliable detection of CTXs, which shows no cross-reactivity with other related marine toxins. This ELISA protocol has been recently improved to exhibit a detection limit (LOD) of less than 1 pg/mL using an alkaline phosphatase-fluorescent system. This detection limit is sufficient to detect very small amount of CTX contaminants in fish, as stipulated by FDA guidance (0.01 ppb=10 ng/kg).² It should be noted that this ELISA method will be useful not only for prevention of CFP but also for the epidemiological and physiological studies.

References:

1. M. Hirama, T. Oishi, H. Uehara, M. Inoue, M. Maruyama, H. Oguri, M. Satake, *Science* **2001**, 294, 1904.
2. M. Hirama, *Proc. Jpn. Acad., Ser. B* **2016**, 92, 290, and cited therein.

Chiral Molecular Science: from the Development of CD Exciton Chirality Method to the Invention of Light Powered Chiral Molecular Motors

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The molecular chirality is a key concept in chemistry, bioscience, and molecular technology like the invention of a light-powered chiral molecular motor explained below. So, the primary subject is how to determine the absolute configuration (AC) of chiral compounds in a reliable manner. There are non-empirical methods for determining ACs of chiral compounds, e.g., the X-ray Bijvoet method and the CD exciton chirality method. In addition, there are relative methods, where the internal reference of AC was used in X-ray and ^1H NMR methods. The author and coworkers have developed these methods and applied to various natural products and chiral synthetic compounds. During these studies, we have also invented light powered chiral molecular motors. These research results will be discussed in this lecture.

1. CD exciton chirality method.

In 1969, Harada and Nakanishi discovered the CD dibenzoate rule for determining the ACs of chiral glycols,¹ as exemplified in Figure 1. This CD method has successfully been applied to various natural products in a reliable manner, because the observed CD showed intense bisignate Cotton effects, and the CD mechanism was established by the exciton theory.^{2,3} The equations for the exciton coupling system are formulated as follows.

α -state:

$$\text{wave function: } \Psi_a^\alpha = (1/\sqrt{2})(\phi_a\phi_{j0} - \phi_{i0}\phi_a)$$

$$\text{energy: } E^\alpha = E_a - V_{ij}$$

$$\text{dipole strength: } D^\alpha = (1/2)(\mu_{i0a} - \mu_{j0a})^2$$

$$\text{rotational strength: } R^\alpha = +(1/2)\pi\sigma_0\mathbf{R}_{ij} \cdot (\mu_{i0a} \times \mu_{j0a})$$

β -state:

$$\text{wave function: } \Psi_a^\beta = (1/\sqrt{2})(\phi_{ia}\phi_{j0} + \phi_{i0}\phi_{ja})$$

$$\text{energy: } E^\beta = E_a + V_{ij}$$

$$\text{dipole strength: } D^\beta = (1/2)(\mu_{i0a} + \mu_{j0a})^2$$

$$\text{rotational strength: } R^\beta = -(1/2)\pi\sigma_0 \mathbf{R}_{ij} \cdot (\mu_{i0a} \times \mu_{j0a})$$

Interaction energy:

$$V_{ij} = R_{ij}^{-3} \{ \mu_{i0a} \cdot \mu_{j0a} - 3R_{ij}^{-2} (\mu_{i0a} \cdot \mathbf{R}_{ij})(\mu_{j0a} \cdot \mathbf{R}_{ij}) \}$$

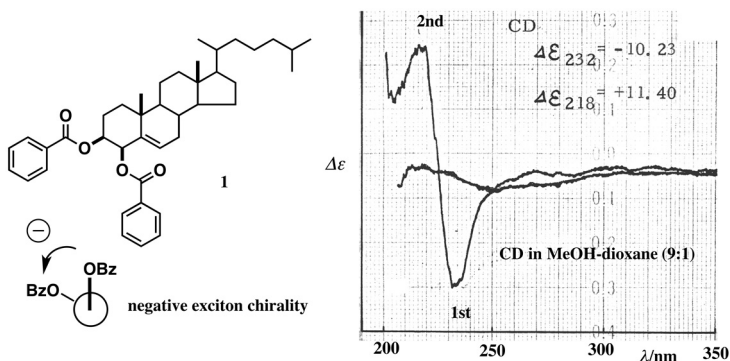


Figure 1. Exciton CD of steroidal dibenzoate **1** and AC determination.

We have also discovered that this CD method is applicable to compounds already possessing a chromophore suitable for exciton coupling. For example, the AC of chromomycin A₃ derivative was determined⁴ as shown in Figure 2, where the transitions of benzoate and naphthalene chromophores couple with each other, making a left-handed helicity, and hence the negative first and positive second Cotton effects were observed. Thus, the dibenzoate rule was generalized as the CD exciton chirality method.

The history of AC determination was also the history of controversies. For example, in the early 1970s, it was claimed that the ACs of compounds (–)-**7** and (+)-**8** shown in Figure 3 assigned by the exciton chirality method disagreed with the ACs determined by the X-ray Bijvoet method applied to their HBr salts, causing big controversies. Furthermore, it was also claimed that the theory of the Bijvoet method was wrong, and hence the ACs determined by the Bijvoet method should be reversed. If so, most textbooks of chemistry had to be revised.

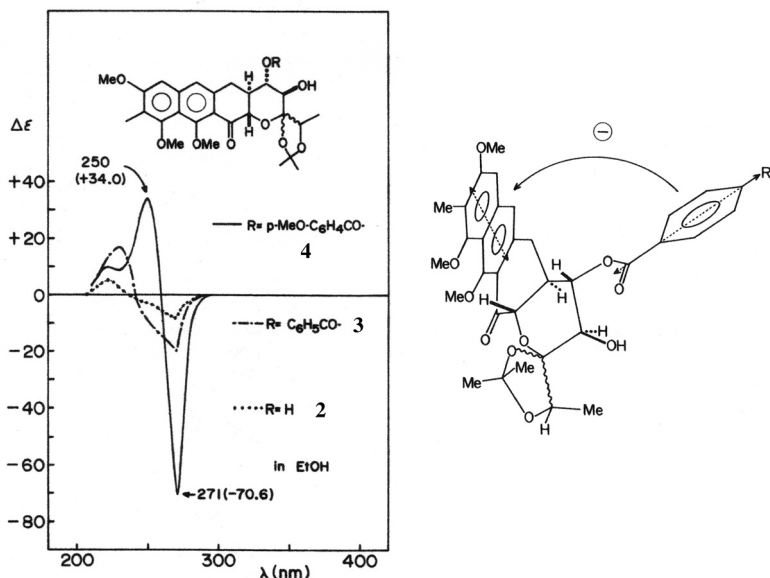


Figure 2. Application of the CD exciton chirality method to chromomycin A₃ derivatives.

To solve this problem, the author and coworkers synthesized the most ideal cage compound (+)-**5** for connecting the CD exciton chirality method and the X-ray Bijvoet method⁵ as shown in Figure 3. The reasons why this compound was selected are as follows: i) in the UV spectrum, an anthracene chromophore exhibits a very intense and long-axis polarized ¹B_b transition at 252 nm (ϵ 204,000); ii) compound (+)-**5** is of cage structure, and hence it has no conformational flexibility; iii) the absolute sense of helicity between two long axes of anthracene chromophores is clear in space; iv) compound (+)-**5** would be synthesized starting from diester (+)-**6**, the AC of which was already assigned by the X-ray Bijvoet method and chemical correlations.

In fact, the CD spectrum of compound (+)-**5** showed very intense exciton split Cotton effects (λ_{ext} 268.0 nm, $\Delta\epsilon$ +931.3 / λ_{ext} 249.7 nm, $\Delta\epsilon$ -720.8), from the signs of which the AC of (+)-**5** was determined as shown in Figure 3. This AC determination agreed with that by the X-ray Bijvoet method. These studies thus put an end to the above controversies.

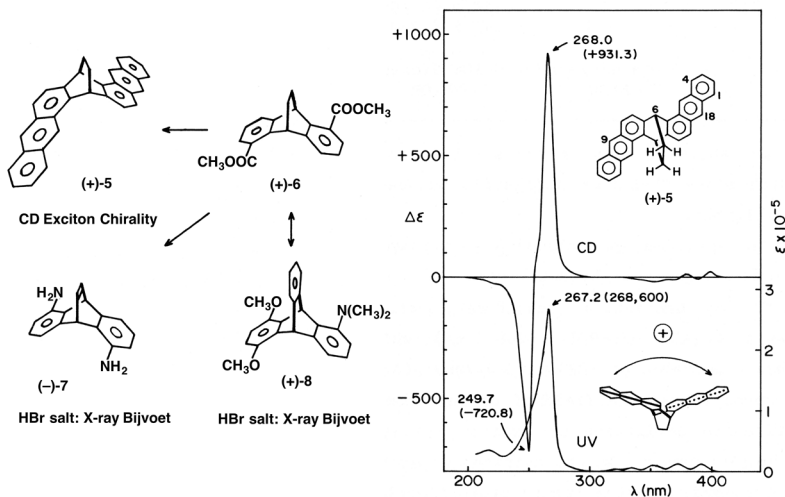


Figure 3. CD and UV spectra of cage compound (+)-5, and consistency between X-ray Bijvoet and CD exciton chirality methods.

2. π -Electron SCF-CI-DV MO method.

The π -electron SCF-CI-DV (Self Consistent Field-Configuration Interaction-Dipole Velocity) MO method is useful for determining the ACs of chiral compounds containing a twisted π -electron conjugated system. For example, derivative (-)-9 of halenaquinol, a marine natural product, contains 1,3-diene unit conjugated with naphthalene ring as shown in Figure 4, where the helicity of π -conjugation system is governed by the chirality at the 12b position. The CD spectrum of compound (-)-9 shows intense Cotton effects, e.g., λ_{ext} 301 nm ($\Delta\epsilon$ -23.3), 229 nm (+40.9), which reflect the helicity of the π -conjugation system.⁶

As the calculation model, compound (12bS)-10 was selected, where the AC was selected at random, and its CD and UV curves were calculated by the SCF-CI-DV MO method. As seen in Figure 4, the basic pattern of CD and UV spectra were well reproduced by the calculation, e.g., λ_{ext} 322 nm ($\Delta\epsilon$ -22.4), 223 nm (+35.5), and therefore, the AC of derivative (-)-9 was determined to be (12bS) as shown. The AC of halenaquinol was clearly assigned.⁶

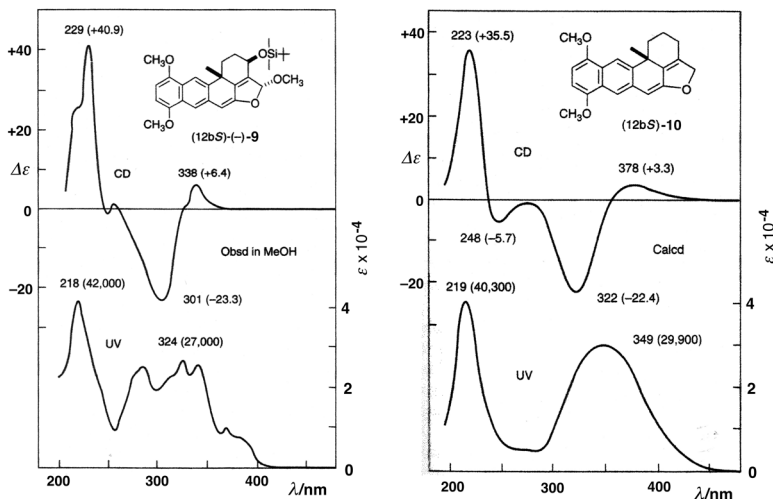


Figure 4. CD and UV spectra of halenaquinol derivative (–)-**9**, and calculated CD and UV curves of model compound **10**.

It is important to prove the theoretically assigned ACs in an experimental manner. So, we attempted the synthesis of halenaquinol; starting from (8*R*)-(–)-Wieland-Miescher ketone, we have first succeeded in the total synthesis of (12*bS*)-(+)-halenaquinol of natural enantiomer via the reactions of 16 steps.⁷ The present results have thus established the reliability of the π -electron SCF-CI-DV MO method.

3. CSDP acid powerful for enantioresolution of alcohols and simultaneous determination of their ACs.

To prepare enantiopure compounds and to determine their ACs simultaneously, we have developed CSDP acid, Camphor-Sultam Dichloro-Phtablic acid, (1*S*,2*R*,4*R*)-(–)-**11** (Figure 5).⁸ For example, racemic alcohol (±)-**12** was esterified with CSDP acid (–)-**11** giving a mixture of diastereomeric esters, which was separated by HPLC on silica gel as shown in Figure 5: separation factor $\alpha = 1.18$. The second-eluted ester (–)-**13b** was obtained as single crystals. Therefore, its AC could be determined by X-ray crystallography as shown in Figure 5, where the CSDP acid part was used as the internal reference of AC. Hydrolysis of ester (3*R*,4*R*)-(+)-**13a** furnished enantiopure alcohol (3*R*,4*R*)-(+)-**12**.⁹ Thus, the advantages of CSDP acid are as follows:⁸ i) its diastereomeric esters are separable by HPLC on silica gel; ii) one of separated esters will be obtained as single crystals suitable for X-

ray analysis in a high probability; iii) CSDP acid moiety can be used as the internal reference of AC.

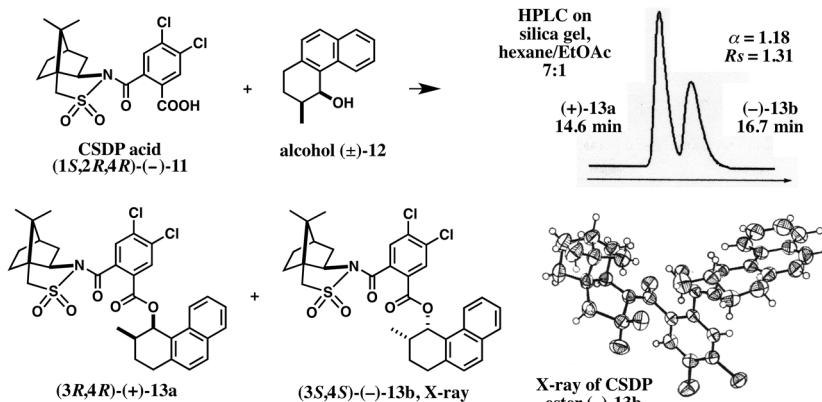


Figure 5. Enantioresolution of racemic alcohol and AC determination by using CSDP acid (1*S*,2*R*,4*R*)-(-)-11.

4. Invention of light-powered chiral molecular motors.

Around 1985, the author was asked by Prof. H. Wynberg, Groningen University, the Netherlands, to determine the ACs of chiral olefins **14** and **15** (Figure 6).

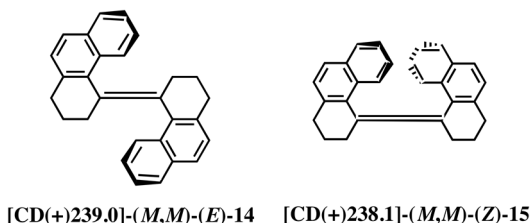


Figure 6. The ACs of chiral olefins **14** and **15** determined by the π -electron SCF-CI-DV MO method.

In these compounds, two naphthalene chromophores conjugate with the central double bond, and the whole π -electron conjugation systems are largely twisted. Therefore, these compounds were ideal systems for the AC determination by the π -electron SCF-CI-DV MO method. By comparing the calculated and observed CD curves, the ACs of chiral olefins **14** and **15** were determined as shown in Figure 6.¹⁰

To confirm the above ACs in an experimental manner, we attempted to synthesize some derivatives containing heavy atoms suitable for the X-ray Bijvoet method. For example, the synthesis of episulfide derivative was attempted, but no desired product was obtained. Therefore, the author changed the strategy as shown in Figure 7, where the synthesis of dimethyl derivatives **17a** and **17c** was planned, expecting that two methyl groups in chiral positions would be useful as the internal reference of AC.⁹

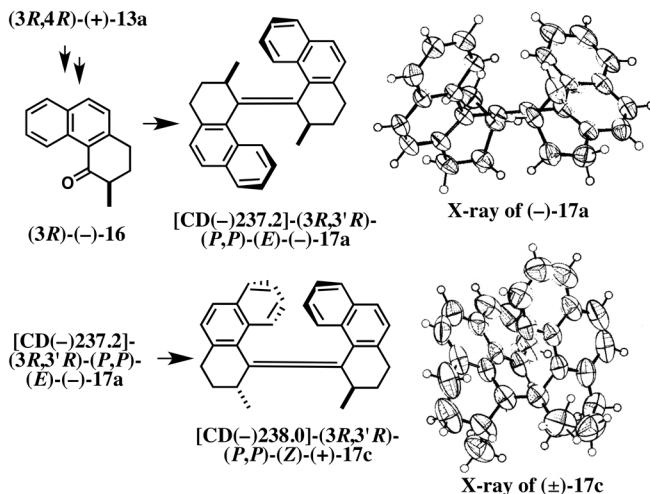


Figure 7. Synthesis of dimethyl derivatives **(-)-17a** and **(+)-17c** and AC determination by X-ray internal reference method.

Starting from CSDP ester **(3R,4R)-(+)-13a** in Figure 5, the desired dimethyl derivative **(E)-(-)-17a** could be synthesized, and its AC could be determined by X-ray crystallography as shown in Figure 7, where two methyl groups were used as the internal reference of AC. The shape and absolute intensity of CD spectrum of compound **[CD(-)237.2]-(3R,3'R)-(P,P)-(E)-(-)-17a** were similar to those of olefin **[CD(+239.0)]-(E)-14**, but CD signs were opposite to each other. Hence, the AC of olefin **[CD(+239.0)]-(E)-14** was established to be **(M,M)**, which confirmed the above AC determination by the π -electron SCF-CI-DV MO method.⁹

The photoreaction of *trans*-olefin **(-)-17a** furnished *cis*-olefin **[CD(-)238.0]-(3R,3'R)-(P,P)-(Z)-(+)-17c**, the AC of which was determined by X-ray analysis of racemate **(±)-17c** as shown in Figure 7, because single crystals of enantiomer **(+)-17c** could not be obtained. Thus, the X-ray analysis of

racemate is also useful for determining AC by the internal reference method. The CD spectra of olefins [CD(−)238.0]-(*Z*)-**17c** and [CD(+)238.1]-(*Z*)-**15** were opposite in sign to each other, and hence the (*M,M*) AC of olefin [CD(+)238.1]-(*Z*)-**15** was established.⁹

During these studies, we have invented a light powered chiral molecular motor as follows.¹¹ Namely, i) compound **17** isomerizes as shown in Figure 8 by photo and thermal reactions; ii) the reaction circulates in one direction, i.e., **17a** → **17b** → **17c** → **17d** → **17a**; iii) during one cycle of reactions, one naphthalene ring rotates 360° in one direction against the other naphthalene ring. Namely, a light powered chiral molecular motor was first synthesized, where the motor mechanically rotates using the light energy, the rotational direction is governed by the molecular chirality, and the motor motion can be controlled by the on/off of light. The key point of the invention was the introduction of two methyl groups.

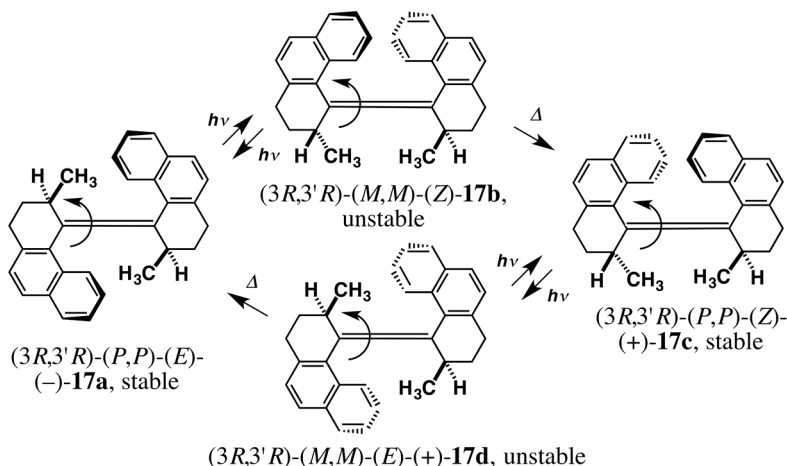


Figure 8. The rotation mechanism of a light powered chiral molecular motor.

It is very interesting and also enjoyable that the basic research of AC determination in an experimental manner created the breakthrough results, which had never been expected at first even by researchers involved.

5. M α NP acid powerful for enantioresolution of alcohols and simultaneous determination of their ACs by ^1H NMR method.

M α NP acid, 2-methoxy-2-(1-naphthyl)propionic acid, (*S*)-(+)-**18** is powerful for enantioresolution of racemic secondary alcohols and also for AC determination by ^1H NMR method as shown in Figure 9.⁸

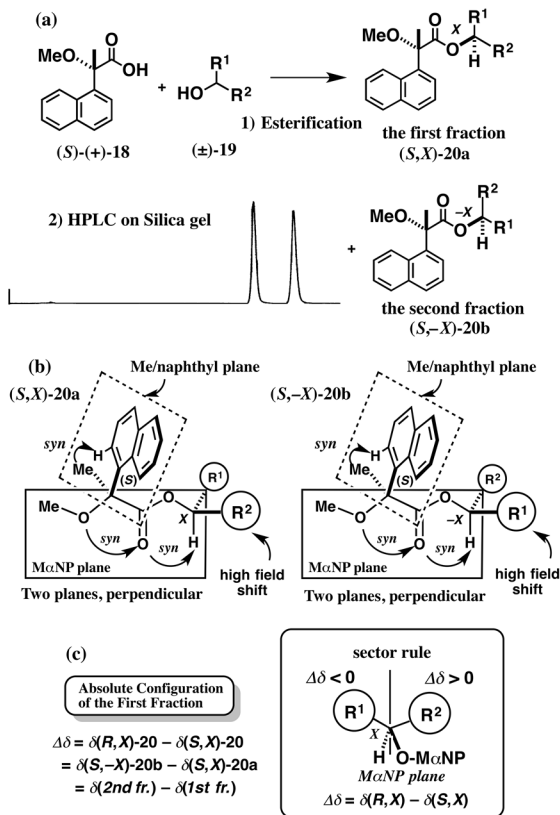


Figure 9. The outline of M α NP acid method.

Racemic secondary alcohol ($\pm$)-**19** is esterified with M α NP acid (*S*)-(+)-**18** yielding diastereomeric esters, which are easily separable by HPLC on silica gel. The first-eluted ester is designated (*S*,*X*)-**20a**, where *S* indicates the AC of acid part, *X* does the AC of alcohol part to be determined. The second-eluted ester is designated (*S*, $-X$)-**20b**, where $-X$ indicates the opposite AC of *X*.

These two esters take the preferred conformations as shown in Figure 9 (b), where in the first-eluted ester (*S,X*)-**20a**, the substituent R² is located over the naphthalene ring, and hence the group R² is high-field shifted in ¹H NMR chemical shift. On the other hand, in the second-eluted ester (*S,-X*)-**20b**, the substituent R¹ is high-field shifted, because it is located over the naphthalene group.

The parameter $\Delta\delta$ is defined as shown in Figure 9 (c), and its value is calculated for each proton from the observed ¹H NMR data. The protons are placed according to the sector rule, where protons with positive $\Delta\delta$ values are placed on the right side, while those with negative $\Delta\delta$ values are placed on the left side. The AC (*X*) of the alcohol part in the first-eluted ester can be thus determined.⁸

The following is a striking example of the M α NP acid method. Racemic acetylene alcohol ($\pm$)-**21** was esterified with M α NP acid (*S*)-(+)-**18** yielding diastereomeric esters **22a** and **22b**, which were largely separated by HPLC on silica gel as shown in Figure 10 (b): separation factor $\alpha = 1.78$. From their ¹H NMR data, the diamagnetic anisotropy parameter $\Delta\delta$ was calculated for each proton as shown in Figure 10 (c), where the acetylene side chain shows positive $\Delta\delta$ values, while the saturated side chain shows negative values. Therefore, the (19*S*) AC was assigned to the first-eluted M α NP ester (–)-**22a**.¹²

To verify the above ACs, we tried to crystallize the esters **22a** and **22b** from various solvents, and finally obtained single crystals of ester (–)-**22b** when recrystallizing from *iso*-PrOH. The crystals were very thin plates with 5 μ m thickness, and hence the strong X-ray of synchrotron radiation at SPring-8 was used. The structure of ester (–)-**22b** was determined as shown in Figure 10 (d): $R = 0.0814$. Although the crystalline state conformation is different from that of the solution state, the AC was unambiguously determined by using the M α NP acid part as the internal reference of AC. The result was in agreement with the AC determined by the ¹H NMR method using M α NP acid. Thus, the ¹H NMR/M α NP acid method was supported by X-ray crystallography.

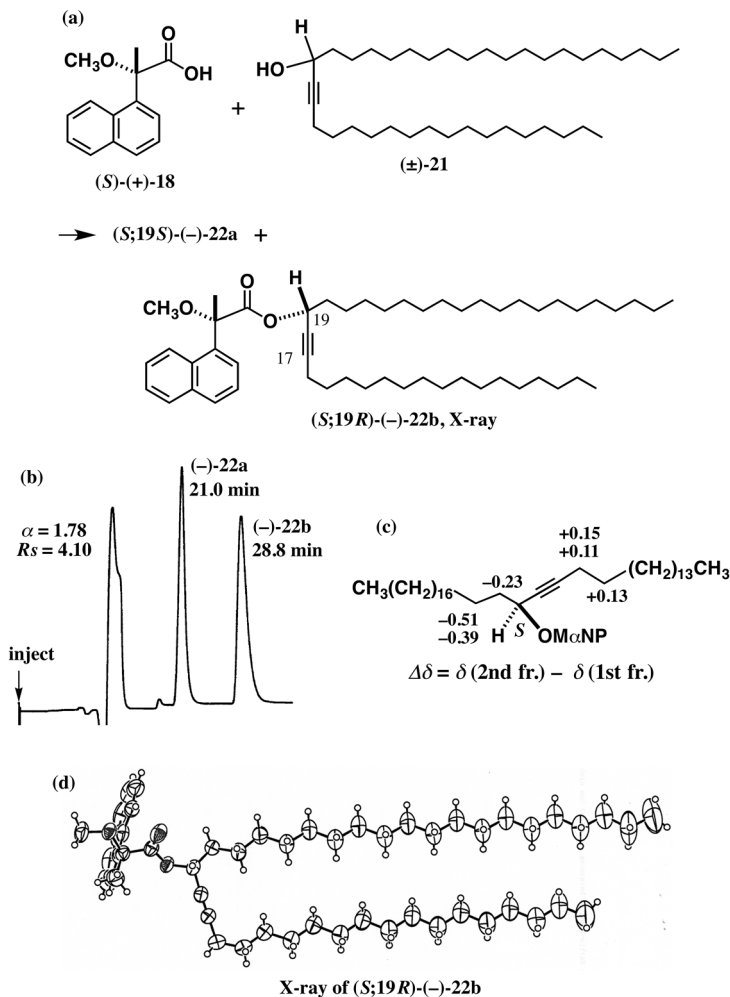


Figure 10. The application of the M α NP acid method to acetylene alcohol **21**.

The hydrolysis of ester (S;19S)-(-)-**22a** yielded enantiopure acetylene alcohol (S)-(-)-**21**, whose AC was unambiguously determined. The M α NP acid method is thus powerful for the preparation of enantiopure alcohols and also for simultaneous determination of their ACs.

Conclusion.

As discussed above, there are several methods for determining the ACs of chiral compounds. When applying these methods, it is important to understand the advantages and disadvantages of each method, and also to evaluate the reliability of the AC assignment carried out. Especially, when the AC was assigned based on the theoretical CD calculation, it is necessary to confirm the AC in an experimental manner.

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The researches discussed in this lecture have been carried out in collaboration with many coworkers, whose names are listed in references. The author sincerely thanks them, especially the staffs and all the students of Harada group, for their efforts.

References:

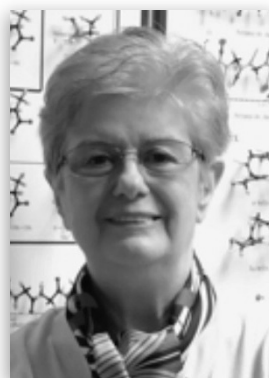
1. A Method for Determining the Chiralities of Optically Active Glycols. N. Harada, K. Nakanishi, *J. Am. Chem. Soc.* **1969**, *91*, 3989.
2. The Exciton Chirality Method and its Application to Configurational and Conformational Studies of Natural Products. N. Harada, K. Nakanishi, *Acc. Chem. Res.* **1972**, *5*, 257.
3. N. Harada, K. Nakanishi, "*Circular Dichroic Spectroscopy – Exciton Coupling in Organic Stereochemistry* –", University Science Books, Mill Valley, California, and Oxford University Press, Oxford (1983).
4. A Method for Determining the Chirality of Two Aromatic Chromophores and the Absolute Configurations of Chromomycin A₃ and Related Antibiotics. N. Harada, K. Nakanishi, S. Tatsuoka, *J. Am. Chem. Soc.* **1969**, *91*, 5896.
5. The Absolute Stereochemistries of 6,15-Dihydro-6,15-ethanonaphtho-[2,3-*c*]-pentaphene and Related Homologues as Determined by both Exciton Chirality and X-ray Bijvoet Methods. N. Harada, Y. Takuma, H. Uda, *J. Am. Chem. Soc.* **1976**, *98*, 5408.
6. Absolute Stereostructures of Halenaquinol and Halenaquinol Sulfate, Pentacyclic Hydroquinones from the Okinawan Marine Sponge *Xestospongia Sagra*, as Determined by Theoretical Calculation of CD Spectra. M. Kobayashi, N. Shimizu, I. Kitagawa, Y. Kyogoku, N. Harada, H. Uda, *Tetrahedron Lett.* **1985**, *26*, 3833.

7. Total Synthesis of (+)-Halenaquinol and (+)-Halenaquinone. Experimental Proof of Their Absolute Stereostructures Theoretically Determined. N. Harada, T. Sugioka, Y. Ando, H. Uda, T. Kuriki, *J. Am. Chem. Soc.* **1988**, *110*, 8483.
8. HPLC Separation of Diastereomers: Chiral Molecular Tools Useful for the Preparation of Enantiopure Compounds and Simultaneous Determination of Their Absolute Configurations. N. Harada, *Molecules* **2016**, *21*, 1328.
9. Chemistry of Unique Chiral Olefins. 3. Synthesis and Absolute Stereochemistry of *trans*- and *cis*-1,1',2,2',3,3',4,4'-Octahydro-3,3'-dimethyl-4,4'-biphenanthrylidenes. N. Harada, N. Koumura, B. L. Feringa, *J. Am. Chem. Soc.* **1997**, *119*, 7256.
10. Chemistry of Unique Chiral Olefins. 1. Synthesis, Enantioresolution, Circular Dichroism, and Theoretical Determination of the Absolute Stereochemistry of *trans*- and *cis*-1,1',2,2',3,3',4,4'-Octahydro-4,4'-biphenanthrylidenes. N. Harada, A. Saito, N. Koumura, H. Uda, B. de Lange, W. F. Jager, H. Wynberg, B. L. Feringa, *J. Am. Chem. Soc.* **1997**, *119*, 7241.
11. Light-driven Monodirectional Molecular Rotor. N. Koumura, R. W. J. Zijlstra, R. A. van Delden, N. Harada, B. L. Feringa, *Nature* **1999**, *401*, 152.
12. Synthesis of Enantiopure Aliphatic Acetylene Alcohols and Determination of Their Absolute Configurations by ^1H NMR Anisotropy and/or X-Ray Crystallography. S. Sekiguchi, M. Akagi, J. Naito, Y. Yamamoto, H. Taji, S. Kuwahara, M. Watanabe, Y. Ozawa, K. Toriumi, N. Harada, *Eur. J. Org. Chem.* **2008**, 2313.

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