EurJOC
European Journal of Organic Chemistry

Minireview
doi.org/10.1002/ejoc.202000711

Chemistry Europe
European Chemical Societies Publishing

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VIP

Determination of the Absolute Configurations of Chiral Alkanes – An Analysis of the Available Tools

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Abstract: Knowledge of absolute configurations (ACs) is crucial to understand the properties and functions of chiral molecules. Although the development of asymmetric reactions has enabled access to a large variety of enantioenriched compounds, stereochemical assignments of chiral molecules, especially chiral alkanes, remain challenging. In this Minireview, we first summarize common analytical techniques for AC determination with a focus on chiral alkanes as analytical targets. Next, we describe some of our efforts over the last 20 years on syntheses and AC determination of chiral alkanes including [123]tetramantane, hexadeuterated neopentane, and *trans*-perhydroazulene. Lastly, microscopic techniques and the crystalline sponge method are discussed as particularly promising approaches to revolutionize the field of stereochemical analysis.

1. Introduction

1.1. Background and Scope of This Minireview

Chirality is a fundamental property of (organic) molecules and is defined as "*the geometric property of a rigid object [•••] of being non-superposable on its mirror image*".[1] The absolute configuration (AC) of this object, e.g., an organic molecule, defines the spatial arrangement of the atoms with stereochemical descriptors *R* and *S*. The AC dictates properties and functions of a chiral molecule, as the two enantiomers interact differently with other chiral molecules or chiral electromagnetic fields like polarized light. This is evident in interactions between chiral molecules (e.g., drugs) and the human body because all receptors are chiral.[2] For example, the two enantiomers of naproxen have drastically different functions: the (*S*)-enantiomer is a commercially available, anti-inflammatory agent, while the (*R*)-enantiomer is a liver toxin. In the case of ethambutol, the (*S*,*S*)-enantiomer can be used to treat tuberculosis, whereas the (*R*,*R*)-enantiomer causes blindness (Figure 1). It is therefore fully understandable that the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) require that, for any chiral drug before coming to the market, the properties of each enantiomer are examined and the ACs are determined.[3,4] It is clear that the control and determination of ACs are both essential to understand the properties and functions of chiral molecules.

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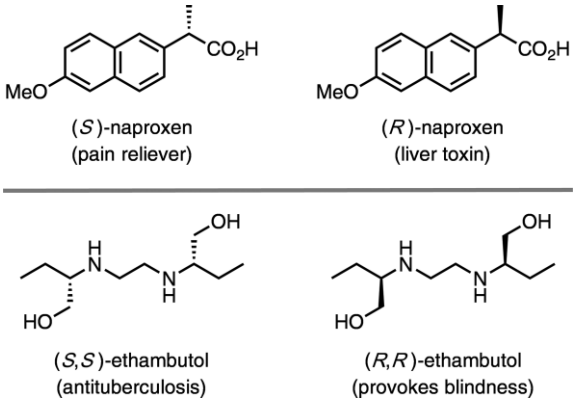


Figure 1. Examples of chiral molecules whose enantiomers function differently.

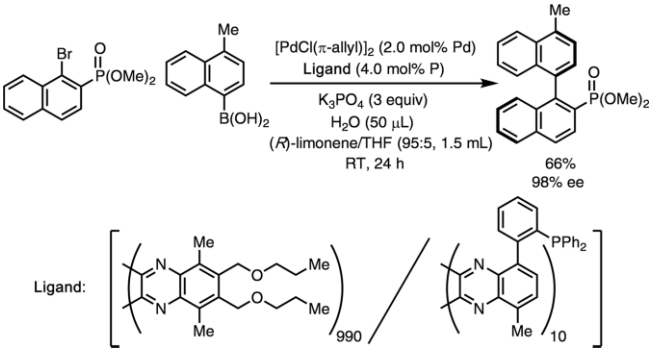
Control of ACs via asymmetric synthesis has been studied extensively over the last few decades, and the number of enantioselective methods is still increasing at a fast pace. In particular, the development of catalytic enantioselective reactions has enabled the synthesis of a myriad of enantioenriched organic compounds. The determination of the ACs of chiral molecules remains a daunting task for organic chemists.[5] This is well illustrated by the fact that in many papers on enantioselective synthesis, the ACs of chiral products are often not determined,[6,7] or at most assigned merely by analogy to the AC of a representative product[8,9] – though a small structural change in a substrate may reverse enantioselectivity of a reaction and preferentially yield the opposite enantiomer.[10,11]

The difficulties associated with AC determination may originate from the lack of a single universal technique that is applicable to all chiral molecules. Hence, it is critical to judiciously select a particular method on the basis of its advantages and disadvantages in analyzing the AC for a particular class of molecules. For this purpose, we first provide a brief summary of currently available analytical techniques for AC determination that may be useful for experimental chemists, thereby focusing on AC assignments of chiral alkanes. We illustrate how those methods can be applied to chiral alkanes by showcasing some of our own efforts over the last 20 years. Finally, we briefly introduce two emerging technologies – visual inspection by microscopic techniques and the crystalline sponge method – that are particularly promising for AC determination of alkanes and in general.

1.2. Why Chiral Alkanes?

The stereochemical analysis of chiral alkanes is of significant importance in various scientific fields.[12,13] In petrochemistry, some chiral alkanes (or more generally hydrocarbons) – formed by removal of functional groups through biological, chemical, and physical processes over time – are known as biomarkers[14] that can be related to functionalized precursors in the source materials such as plants and bacteria.[15] Stereochemical analysis of such chiral alkanes in, for example, petroleum may provide information on the source, maturity, and migration of the hydrocarbon resource. In astrobiology, structural analysis of chiral alkanes might play a pivotal role in a search for extraterrestrial homochirality because some chiral alkanes appear to constitute organic components in Saturn's largest satellite Titan.[16]

The potential utility of chiral alkanes may extend to organic synthesis. As alkanes are generally unreactive, their usage as solvents is highly advantageous. Recently, Suginome demonstrated that a helical catalyst whose helicity is induced by a chiral solvent (limonene) can be utilized for palladium-catalyzed asymmetric reactions including Suzuki–Miyaura cross-coupling (Scheme 1).[17] This finding together with a study by Yashima on helix formation induced by chiral alkanes[18] may open the door to the use of chiral alkanes as chirality transfer (co)solvents or additives in asymmetric reactions.



Scheme 1. Asymmetric Suzuki–Miyaura cross-coupling in a chiral solvent.

Note that stereochemical information of alkanes is crucial for any purposes presented above. In an introductory organic chemistry class, undergraduate students are frequently asked, "what is the simplest chiral alkane?" The typical answer is 3-methylhexane shown in Figure 2. This communication is usually not followed by a question: "how would you determine the AC of 3-methylhexane?" This is not a trivial question; in fact, chiral alkanes are one of the most challenging structural classes for stereochemical analysis because alkanes bear no classic chromophores that often are the basis for AC assignment; they also lack polar functional groups for derivatization and are often conformationally flexible. These features often lead to very small specific optical rotations ($[\alpha]_D^{25} \approx 0$), a phenomenon called crypto-optical activity[19] (or cryptochiral, a misnomer because the chirality still persists).[20] Hence, the AC assignment of (crypto-optically active) alkanes are a formidable analytical challenge.

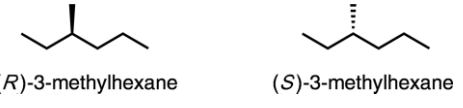


Figure 2. Enantiomers of 3-methylhexane.

2. Overview of Analytical Methods for AC Determination

Table 1. summarizes commonly used analytical methods for AC determination, providing an assessment of the advantages and

Table 1. Overview of analytical techniques commonly employed for AC assignment.

Technique	Accessibility of instrument	Typically required atom/ functional group	Drawbacks	Applicable to alkanes?
X-ray	high	heavy atom	Good single crystals needed	rarely
Mosher NMR	high	alcohol, amine, carboxylic acid	Specific functional groups (left) needed.	no
ORD	high	–	Reasonably large specific rotation ($[\alpha]_D$ > 10) preferred	sometimes
ECD	moderate	chromophore	Absorption in the UV/Vis region needed	no
VCD	low	–	Low signal intensities require long data accumulation time and high sample concentration	yes
ROA	very low	–	Spectrometers not readily available	yes

disadvantages of each method. Note that we take AC determination of chiral alkanes into particular consideration.

Especially synthetic chemists may consider chemical derivatization to a compound of known AC as a viable technique; this is indeed one way to assign the AC of some chiral molecules. However, the applicability of this method is severely limited, as 1) not all molecules can be derivatized into a compound of known AC, 2) the derivatization may require multiple, possibly inefficient steps, 3) the derivatization may affect the stereogenic center(s), and 4) any contamination of chiral molecules caused by the chemical transformation(s) may significantly influence the specific rotation of the derivatized compound. It is therefore highly desirable that stereochemical analysis is performed directly for a compound whose AC is of interest (i.e., without chemical derivatization).

2.1. Single Crystal X-ray Analysis

Single crystal X-ray diffraction analysis is undoubtedly the most powerful method for AC determination.[21,22] The absolute structure of a crystalline compound can be solved under conditions of anomalous dispersion (the Bijvoet method).[23] Anomalous dispersion occurs when the X-ray energy is close to the absorption edge of a specific element in the structure, which results in different reflection intensities with indices *hkl* and *–h–k–l*. If the calculated intensity difference for a given model (e.g., *I*(*hkl*) > *I*(*–h–k–l*)) is identical to that obtained from experiment, the model structure has the correct AC. If not identical, the AC of the sample is that of the mirror image of the model structure. As anomalous dispersion increases with the atomic number, the presence of heavy atom(s) (e.g., S, P, and halogens) in the analyte molecule is usually required to apply this technique. Alternatively, the AC of a chiral compound can also be indirectly determined with the assistance of an enantiopure compound of known AC (e.g., chiral resolving agents from natural products) if the analyte substance forms an ionic[24,25] or covalent bond[26,27] with a reference compound. Crystallization of the resulting compound enables one to deduce the AC of the analyte molecule from that of the chiral agent.

As the name implies, single crystals of good quality are essential for this analysis. Growing good single crystals is often an extremely demanding task, as it requires not only elaborate crystallization techniques,[28] but also patience and luck. Frequently, one may obtain suitable crystals for analysis only after considerable trial and error. Although recent technological advance – especially the use of CuK_α radiation – has shown that even the AC of alkanes can be determined,[29] the presence of a heavy atom or a functional group facilitates the X-ray analysis by strong anomalous dispersion or the derivatization with a chiral reference compound, respectively.

2.2. Mosher Analysis

Derivatization with an enantiopure compound of known AC also aids the AC determination by NMR analysis.[30,31] α-Methoxy-α-trifluoromethylphenylacetic acid (MTPA, **1**), also known as Mosher's acid, is commercially available in both enantiomeric forms and is currently the most popular – though not always the optimal – chiral derivatizing agent (Figure 3A). When enantiomerically pure MTPA reacts with, e.g., a chiral secondary alcohol **2**, a pair of diastereomeric MTPA esters **3** forms and can be analyzed by NMR. When Mosher's acid chloride (MTPA-Cl) is used for derivatization, one must note that the *R*-enantiomer of MTPA-Cl gives rise to the *S*-enantiomer of MTPA ester and vice versa.

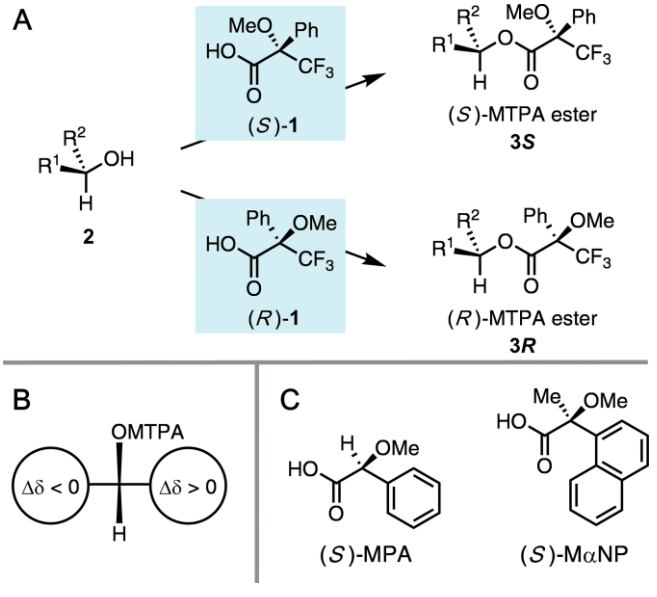


Figure 3. (A) Synthesis of MTPA esters, **3*S*,** and **3*R***. (B) Model to assign the AC of **2** based on chemical shift difference $\Delta\delta$ (= δ_S – δ_R). (C) Chiral derivatizing agents (*S*)-MPA and (*S*)-MαNP.

Initially demonstrated by Mosher[32] and later revised by Kakisawa and Kusumi,[33] the analysis is carried out as follows: 1) assign as many proton resonances as possible in the two diastereomers **3**; 2) calculate $\Delta\delta$ (= δ_S – δ_R) for as many protons

as possible where δ_S and δ_R are the chemical shift of the (*S*)- and (*R*)-MTPA esters, respectively; 3) determine the AC applying the model in Figure 3B. The analysis is based on the assumption that the MTPA esters adopt a particular conformation as shown in Figure 3A, where the ester displays an *s-trans* arrangement about its O–CO bond, and where both the CF_3 substituent and the methine proton of the secondary alcohol are *syn*-coplanar with the carbonyl group. In this conformation, a more upfield chemical shift is observed for proton(s) on the side of the phenyl substituent of MTPA due to the anisotropic, magnetic shielding effect, which contributes to δ. When a Mosher ester cannot adopt this particular conformation (e.g., when using a sterically hindered alcohol),[34] the model in Figure 3B may not be applied owing to the small and randomly distributed $\Delta\delta$ values.[35] If, on the other hand, the $\Delta\delta$ values are sufficiently large and show a reasonable distribution pattern, one can expect a reliable AC assignment. This procedure is, however, only applicable to secondary alcohols (and less commonly amines[36] and carboxylic acids[37]), and the ACs of other stereogenic centers, if any, in the same molecule need to be assigned by, e.g., analysis of coupling constants.

There are other chiral derivatizing agents available such as α-methoxy-α-phenylacetic acid (MPA)[38] and 2-methoxy-2-(1-naphthyl)propionic acid (MαNP) in Figure 3C.[39,40] These reagents work with the same principle as MTPA and provide some advantages. A study by Riguera et al. showed that the use of MPA leads to larger $\Delta\delta$ values and more reliable AC assignments than MTPA when analyzing secondary alcohols.[41] Harada demonstrated the utility of MαNP (or MPA) as chiral resolving agents; the two diastereomers formed between enantiopure MαNP (or MPA) and racemic menthol are separated by HPLC, while the diastereomeric MTPA esters are not.[39] A further advantage of MαNP is a stronger anisotropic effect of the naphthyl group than the phenyl group in MTPA, resulting in larger $\Delta\delta$ values. A drawback of MPA is the possible racemization of the tertiary carbon stereogenic center, and MαNP is more costly than MTPA and MPA.

No need for crystallization and the broad availability of NMR spectrometers are advantages of this technique. However, application to alkanes is not practical because the incorporation of the necessary functional group is synthetically challenging.

2.3. Optical Rotatory Dispersion (ORD)

Optical rotation is the outcome of unequal velocities of right and left circularly polarized light that passes through a chiral solute in an inert solvent; optical rotation measurement of solids is rare.[42] The measurement of optical rotation at the Na-D-line (589 nm) is a routine task when characterizing a new chiral compound for publication ("specific rotation"). ORD is the variation of the optical rotation with a change of the wavelength of the light employed, and a curve results from plotting optical rotations against wavelengths.[43–45] The shape of the curve is often characterized by positive and/or negative "Cotton effects".[46] When a substance absorbs plane-polarized light, a Cotton effect is the significant change in the optical rotation near its absorption band. A positive (or negative) Cotton effect is observed when the optical rotation reaches a maximum and then a minimum (or a minimum and then a maximum) with decreasing wavelengths. A comparison between experimental and computed ORD[47–49] is a way to assign the AC. This approach, especially for quantitative comparisons, should ideally be performed by measuring intrinsic rotations (i.e., specific rotations at infinite dilution where there is no influence of solute-solute interactions) because computations of specific rotations are usually performed for isolated molecules.[50]

There are notable advantages for ORD including 1) a polarimeter is available in most organic chemistry laboratories, 2) computation of optical rotations can be readily executed, 3) there is no need for a particular atom/functional group for ORD measurement. Due to these features, ORD can be the most convenient approach to assign the AC, especially for conformationally rigid molecules with relatively few low energy conformers. Stephens et al. demonstrated that the ACs of numerous polycyclic alkanes can be reliably assigned by matching experimental and computed optical rotations.[51,52] For flexible molecules, however, one has to take particular care of the conformer distributions because even small geometric changes can lead to significant differences in optical rotation. It is important to compute accurate relative conformational energies to generate the computed Boltzmann averaged ORD spectrum. ORD is influenced by multiple factors such as temperature, concentration, adventitious chiral impurities, and solvents. As observed for propylene oxide, different solvents can even lead to the opposite sign of optical rotations.[53] Owing to the sensitivity to these factors, the AC assigned by ORD should be solidified by other techniques.

2.4. Electronic Circular Dichroism (ECD)

A chiral substance does not only refract but also absorbs right and left circularly polarized light to different extents. The difference in absorption can be measured as a function of wavelength, which provides an ECD spectrum. Just as ORD, the spectrum may exhibit positive and/or negative Cotton effects and a comparison between experimental and computed ECD spectra allows the AC assignment of the sample.[54,55] Note, however, that the measurement of ECD requires the presence of a chromophore that absorbs light in the applied (typically UV/Vis) wavelength range. This technique is therefore not directly applicable to simple chiral alkanes.

2.5. Vibrational Circular Dichroism (VCD)

VCD spectroscopy records the difference in absorption from right and left circularly polarized IR radiation,[56,57] making it the chiral version of well-known IR spectroscopy. As all chiral molecules are IR active, VCD spectroscopy is, in principle, applicable to every chiral molecule irrespective of its physical state. The spectrum is measured as either neat or a solution in an inert solvent such as CCl_4 and $CDCl_3$, which do not strongly interact with the sample. Measurements can also be performed for chiral compounds in the gas phase. The assignment of the AC is performed by matching the measured and computed VCD

spectra with respect to sign, wavenumber, and intensity. In contrast to ORD and ECD, a VCD spectrum typically exhibits many characteristic peaks (VCD Cotton effects) that ensure a more reliable AC assignment. In case the target molecule adopts multiple conformations, one must take the Boltzmann distribution into account to simulate the computed VCD spectrum. One drawback of VCD is low signal intensities, typically ranging from 10^{-4} to 10^{-5} absorption units. This, compared to ECD, for example, requires long data accumulation time (hours) and relatively high sample concentrations (1–50 mg mL^{-1}).[58] Another disadvantage is limited availability of VCD spectrometers, which hampers the wide application of this technique.

Still, this increasingly popular technique has been successfully implemented for the AC determination of numerous molecules.[59] A remarkable example is the AC determination of 4-ethyl-4-methyloctane (**4**, Figure 4A).[60] The stereochemical analysis of **4** is extremely challenging; **4** does not possess any atom or functional group required for anomalous dispersion X-ray crystallography, Mosher NMR analysis, or ECD. Furthermore, the specific rotation of **4** is nearly zero because 1) the number of carbon atoms between the four alkyl substituents is different only by one or two, and 2) the same four methylene groups are located adjacent to the quaternary stereogenic carbon.[61] Harada's approach to the AC determination of **4** was VCD spectroscopy (Figure 4B). After careful consideration of all conformers of **4**, the computed and measured VCD spectra showed excellent agreement, which allowed unambiguous AC assignments of (*S*)-(–)-**4** (and (*R*)-(+)-**4**).

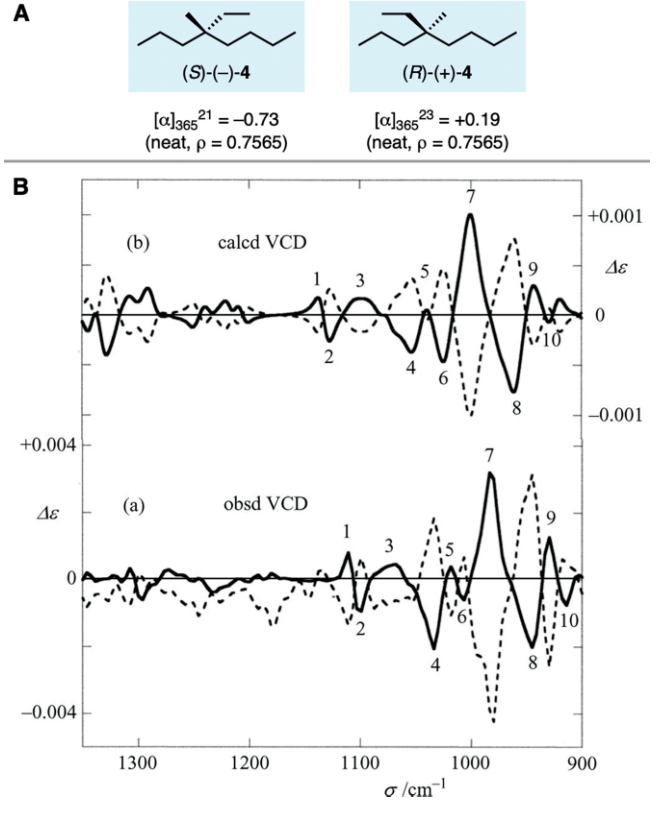


Figure 4. (A) Enantiomers of 4-ethyl-4-methyloctane (**4**) and their measured specific rotations. (B) (a) Observed VCD spectra of (*S*)-(–)-**4** (neat, solid line) and (*R*)-(+)-**4** (neat, dotted line). (b) Computed VCD spectra of (*S*)-**4** (solid line) and (*R*)-**4** (dotted line). The numbers indicated on the solid lines specify VCD Cotton effects and show the one-to-one correspondence between experimental and theoretical VCD bands. The VCD spectra were reprinted from ref.[60]

2.6. Raman Optical Activity (ROA)

Similar to the relationship between VCD and IR spectroscopy, Raman optical activity (ROA) is the chiral variant of Raman spectroscopy.[62,63] The ROA technique measures unequal intensities of Raman scattered light resulting from the transmission of right and left circularly polarized light passing through a neat (gas, liquid, or solid) chiral sample or a solution containing a chiral substance. The AC is assigned by comparing the measured and computationally simulated ROA spectra. A report in 1997 demonstrated the AC assignment of bromochlorofluoromethane (**5**) with this approach.[64] Like the VCD technique, ROA spectra are accompanied by low signal intensities. Accessibility to ROA spectrometers is even more limited, and the application of ROA currently lags behind that of VCD.[65]

In 2007, Bochet and Hug disclosed an excellent application of ROA through the AC determination of suitably deuterated neopentane $C(CH_3)(CH_2{}^2H)(CH^2H_2)(C^2H_3)$, henceforth referred to as $^2H_6$-**6** (Figure 5).[66] Being a prototype of chiral molecules whose chirality is only due to an asymmetric mass distribution, $^2H_6$-**6** is electronically achiral within the Born-Oppenheimer approximation. Hence, electron excitation methods such as ORD and ECD are not expected to be applicable, and the AC determination of $^2H_6$-**6** presented a formidable task. Following the elegant synthesis of (*S*)-$^2H_6$-**6**, which itself was a challenge, the AC was unambiguously assigned by matching experimental and DFT computed ROA spectra. Our complementary approach to the AC determination of $^2H_6$-**6** utilizing VCD spectroscopy is presented in the following section.

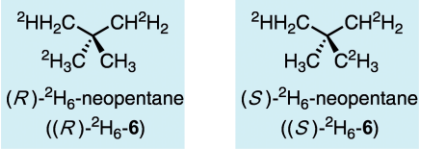


Figure 5. Enantiomers of hexadeuterated neopentane $^2H_6$-**6**.

3. AC Determination of Chiral Alkanes

Simple alkanes offer opportunities to study the most fundamental aspects of molecules such as bonding, reactivity, structure, and chirality. Notwithstanding the notable examples presented above, AC assignment of alkanes are not straightforward. In the following, we present some of our work on AC determination of alkanes to demonstrate successful applications of the analytical techniques introduced in the preceding section. We also describe syntheses of the chiral alkanes that posed unique synthetic challenges.

3.1. Polyhaloadamantanes and Polyhalocubanes

Conformationally rigid pseudotetrahedral molecules are promising candidates for experimentally probing the effects of

molecular parity violation (i.e., enantiomers do *not* have the same energy).[67] The archetypal pseudotetrahedral molecule bromochlorofluoromethane (**5**, Figure 6A)[68] is not particularly suitable for such studies owing to the lack of configurational stability during its synthesis.[69] On the other hand, polyhaloadamantanes **7**–**9**[70] and polyhalocubanes **10**–**12**[71] constitute a class of pseudotetrahedral compounds without atoms at their stereogenic centers and possess conformational rigidity and configurational stability. Although they are substituted alkanes, we include studies on these structures as one of our earliest examples whose ACs were determined.

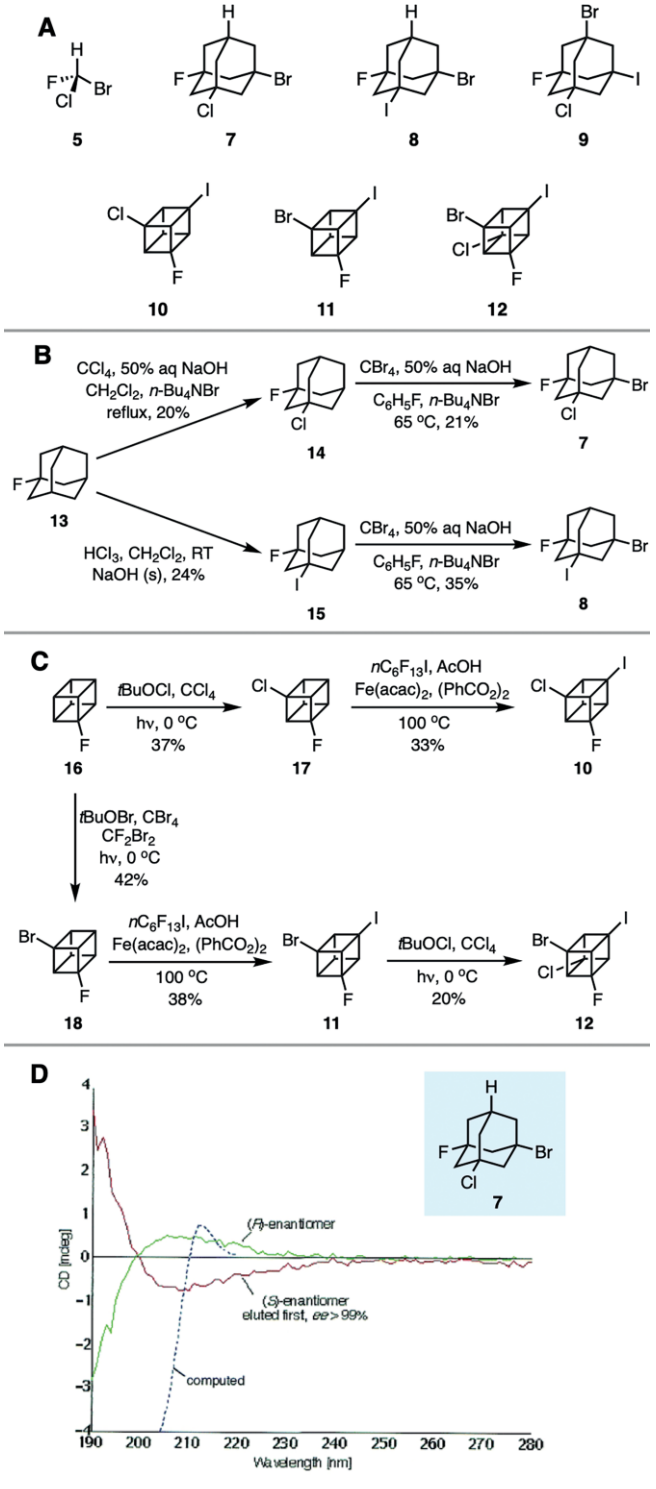


Figure 6. (A) Examples of conformationally rigid pseudotetrahedral molecules. (B) Synthesis of polyhaloadamantanes. (C) Synthesis of polyhalocubanes. (D) AC assignment of trihaloadamantane **7** by ECD spectroscopy. The ECD spectra were reprinted with permission from ref.[70] Copyright 2002 American Chemical Society.

In the late 1990s, we developed site-selective C–H halogenation reactions of unactivated alkanes including adamantane.[72–74] The implementation of these methods allowed us to iteratively incorporate halogen substituents into adamantane scaffolds to synthesize tri- and tetrahalogen-substituted adamantanes **7**–**9** (Figure 6B).[70] After considerable efforts, we successfully separated the two enantiomers of **7** and **8** by chiral HPLC. Later, the iterative halogenation strategy was extended to the synthesis of polyhalocubanes including **10**–**12** (Figure 6C); in this case, however, the near-spherical shape of polyhalocubanes did not allow their enantioseparation by HPLC.[71]

Unsurprisingly, the specific rotation of enantiopure **7** was very small ($[\alpha]_D^{25} \approx 1°$), which made its AC determination solely by matching the experimentally measured and computed specific rotations quite unreliable. On the other hand, the ECD spectra of **7** showed appreciable intensities in the range of 190–240 nm (Figure 6D). We computed the ECD spectrum of the (*R*)-enantiomer at DFT/CI-B3LYP/TZVP//B3LYP/6-31+G(d,p), which agrees qualitatively with the experimental spectrum of the second eluted enantiomer that showed a positive sign (+) in the optical rotation measurement; the AC of trihaloadamantane **7** was assigned as (*R*)-(+)-**7**. Following a similar procedure, the AC of (*R*)-(–)-**8** was also determined.

3.2. [*n*]Triangulanes

[*n*]Triangulanes (**19**) consist of spiroannelated and thereby mutually orthogonal cyclopropane rings (Figure 7A).[75] Depending on how the cyclopropane rings are assembled, [*n*]triangulanes ($n \geq 4$) exhibit helical chirality and constitute rare examples of σ-[*n*]helicenes, the σ bond analogs of well-known aromatic [*n*]helicenes (better called π-[*n*]helicenes). We were intrigued not only by studying optical rotatory strengths due to the molecular helicity but also synthetic challenges to prepare enantiomerically pure [*n*]triangulanes.

Although synthesis of racemic [4]triangulane (**20**), as well as that of racemic [5]triangulane (**21**) as a mixture with its meso isomer **22**, were documented in 1990,[76] the preparation of enantiomerically pure [*n*]triangulanes had yet to be realized; this was accomplished in the de Meijere group. To synthesize enantiopure **20**, the enantioseparation was carried out at an early stage of the synthesis by forming dehydroabietylamine salts of **23** and their recrystallization (Figure 7B);[19,77] following the formation of ethyl ester **24**, cyclopropanation afforded the [3]triangulane derivative **25** (Figure 7C). Reduction, bromination, followed by base-mediated elimination gave olefin **27**, which was subjected to cyclopropanation to furnish [4]triangulane (**20**) in enantiopure form. A similar reaction sequence allowed elongation of the spirocyclic assembly to synthesize enantiopure [5]triangulane (**21**, Figure 7D).

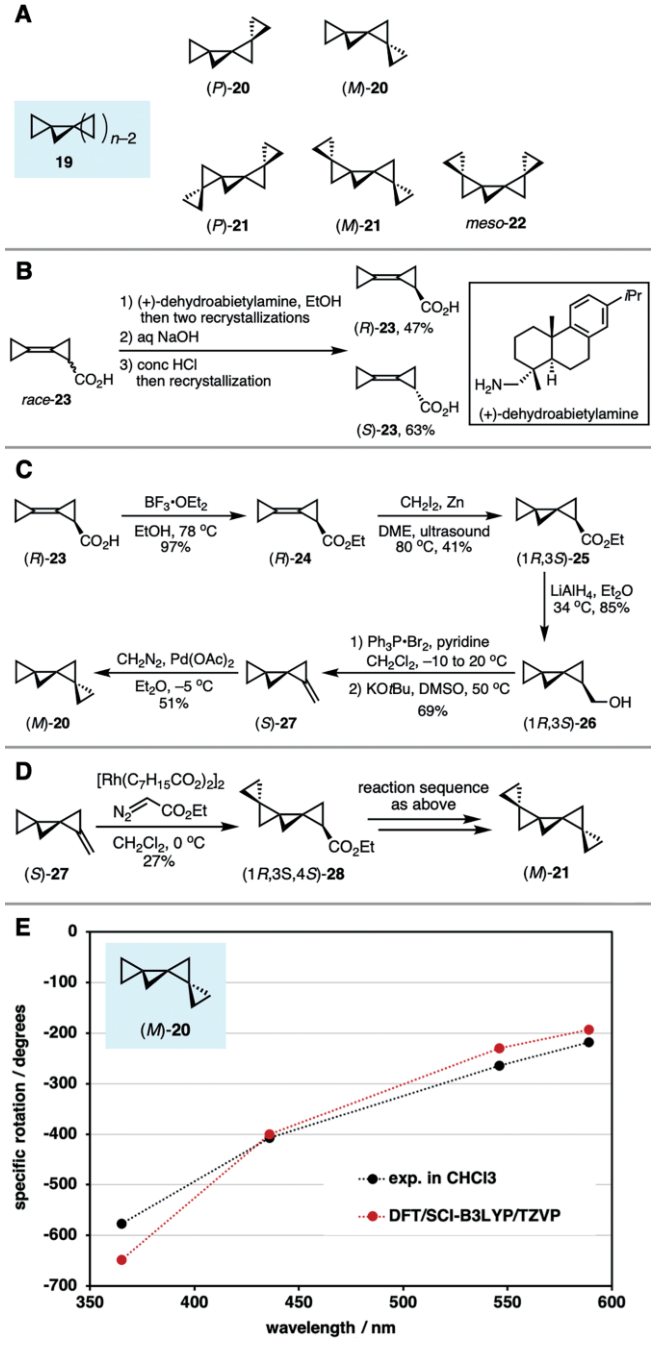


Figure 7. (A) Structures of [*n*]triangulanes. (B) Resolution of carboxylic acid **23** with dehydroabietylamine. (C) Synthesis of [4]triangulane (**20**). (D) Synthesis of [5]triangulane (**21**). (E) AC assignment of **20** by ORD.

Notably, enantiopure **20** displays exceptionally large specific rotation ($[\alpha]_D^{25} = -192.7$) despite the fact that **20** does not have significant absorptions above 200 nm. As shown in Figure 7E, the measured ORD is in good agreement with the computed ORD at DFT/SCI-B3LYP/TZVP//B3LYP/6-31+G(d,p).[77] The ORD computed later at the more sophisticated CCSD/aug-cc-pVDZ//B3LYP/6-31G(d) level of theory showed even better agreement with the experimental ORD.[78] The AC assigned based on these ORD data is fully consistent with the known AC of the synthetic intermediates such as **25**.

3.3. [123]Tetramantane

In 2009, we documented the parent of a new family of σ-helicenes based on non-spirocyclic scaffolds: [123]tetramantane (**29**, Figure 8A).[79] As the name infers, tetramantanes are rigid carbon-based structures consisting of four adamantane units. There are three isomeric structures of tetramantanes: 1) helical [123]tetramantane (**29**) with C_2 symmetry, 2) rod-shaped [121]tetramantane (**30**) with C_{2h} symmetry, and 3) disk-like [1(2)3]tetramantane (**31**) with C_{3v} symmetry. For our study, we isolated both enantiomers of **29** from petroleum by multiple chiral HPLC separations.

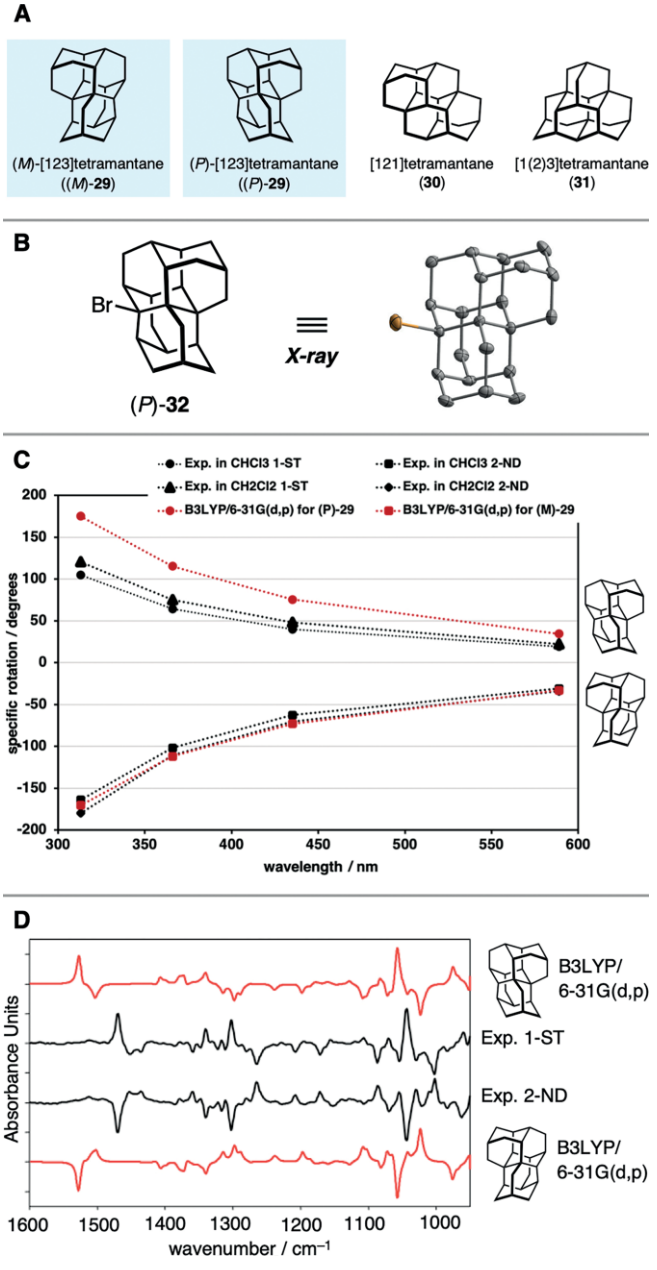


Figure 8. (A) Tetramantane isomers. (B) X-ray structure of monobromo [123]tetramantane (*P*)-**32**. (C) AC assignment of **29** by ORD. 1-ST and 2-ND mean the first and second eluted enantiomers (by HPLC), respectively. (D) AC assignment of **29** by VCD. The VCD spectra were reprinted with permission from ref.[79] Copyright 2009 American Chemical Society.

We employed three independent methods to assign the AC of **29** – that is, X-ray crystallographic analysis, ORD, and VCD spectroscopy. For X-ray analysis, we first derivatized **29** into its bromide **32**; bromination (Br_2 in CH_2Cl_2) preferentially occurred at the C^7-H position to give monobromo compound **32** in 37% yield after two recrystallizations from *n*-hexane. Single crystals of **32** was analyzed by X-ray diffraction under anomalous dispersion conditions (Figure 8B). Based on the resolved X-ray structure, we assigned the AC of **32** as (*P*)-(+) and thus deduced the AC of **29** as (*P*)-(+).

Next, we applied ORD to confirm our AC assignment of **29**. Specific rotations at 589, 435, 366, and 313 nm were measured for both enantiomers. We also computed the specific rotations at B3LYP/6-31G(d,p). The agreement between experiment and theory is remarkable (Figure 8C): 1) the absolute values of the specific rotation increase with decreasing wavelengths and 2) the measured specific rotations agreed almost perfectly with the computations especially for the second eluted enantiomer, presumably because it has higher purity than the first eluted enantiomer. Similar ORD analysis of **32** also revealed an excellent agreement between experiment and theory. The results of ORD, therefore, strongly supported our AC assignment as (*P*)-(+)-**29**.

As the third method, we utilized VCD spectroscopy. The experimental VCD spectrum of (+)-**29** was compared with the B3LYP/6-31G(d,p) computed VCD spectrum of (*P*)-**29** in the 1600–1000 cm^{-1} range (Figure 8D), as the C–H absorption region was poorly resolved in the spectrum. There is good correspondence between the measured and computed VCD spectra with respect to major positive and negative VCD Cotton effects, which solidified our AC assignment of (*P*)-(+)-**29**.

3.4. $^2H_6$-Neopentane

In 2015, we presented the AC assignment of hexadeuterated neopentane $^2H_6$-**6** employing VCD spectroscopy.[80] An alternative enantioselective synthesis of (*S*)-$^2H_6$-**6** was carried out in the Marek group using alkylidenecyclopropane (*S*)-**33**[81] as the starting point (Figure 9A). When reacted with the Negishi zirconocene reagent,[82] (*S*)-**33** underwent allylic C–H bond activation followed by selective C–C bond cleavage.[83] The resulting bis-metallated species were quenched with ^2H_3O to give acyclic intermediate (*R*)-**34**. Ozonolysis and ^2H incorporation through reduction steps furnished elusive (*S*)-$^2H_6$-**6**. Starting with (*R*)-**33**, the opposite enantiomer (*R*)-$^2H_6$-**6** was also prepared. Although the large and well-resolved IR signals were observed in C–H and C–D stretching absorption regions, all VCD signal intensities in this region cancel due to the presence of nine energetically close-lying conformers! Nonetheless, the VCD spectrum measured at 8 K ($^2H_6$-**6** isolated in an Ar matrix) showed appreciable peak intensities in the fingerprint region (1500–1000 cm^{-1}). Agreement with the VCD spectrum computed at B3LYP/aug-cc-pVTZ allowed us with confidence to assign the AC (Figure 9B) which was indeed identical to the AC deduced from the synthesis.

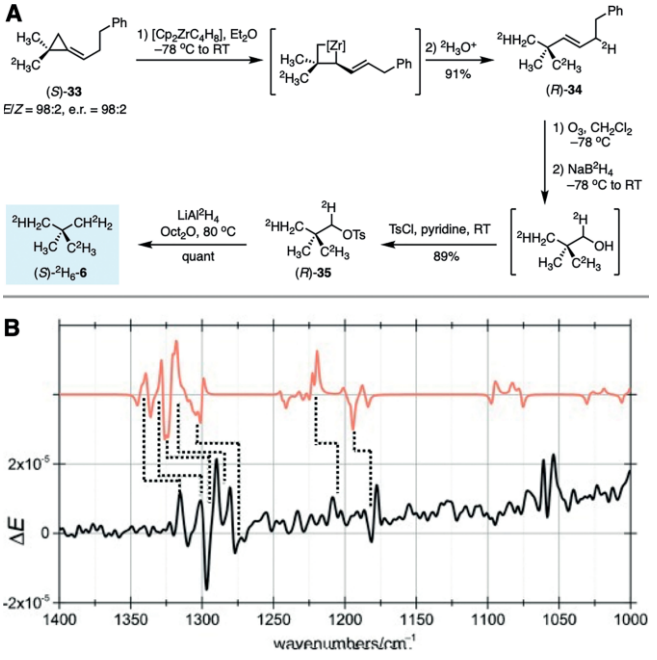


Figure 9. (A) Enantioselective synthesis of hexadeuterated neopentane $^2H_6$-**6**. (B) AC determination of $^2H_6$-**6** by matching measured (black) and computed (B3LYP/aug-cc-pVTZ, orange) VCD spectra. The VCD spectra were reprinted from ref.[80]

3.5. Perhydroazulene

Perhydroazulenes display the [5,7] fused bicyclic system and are common structural motifs in many terpene natural products.[84] The two diastereomers **36** and **37** (Figure 10A) are thus the parent of all perhydroazulene terpenoids although studies on these key structures are extremely scarce. Recently we disclosed the (racemic) synthesis of **36** and **37** based on new strategies.[85] We also performed conformational analysis of **36** and **37**, which revealed the unexpected higher stability of the *cis* isomer at ambient temperatures. Despite the structural importance, **36** had not been prepared in an enantiopure form and the AC was thus far unknown. We, therefore, turned our focus on AC determination of **36**.[86] Our initial efforts to separate the two enantiomers of **36** by chiral HPLC were unsuccessful. As a consequence, we carried out the synthesis of enantiomerically pure **36** following the route depicted in Figure 10B. The resolution of racemic dicarboxylic acid **38** with quinine provided (–)-**39** with 99% ee after five recrystallizations from ethanol. Further transformations involving the Thorpe-Ziegler reaction[87] and a modified Wolff-Kishner reduction[88] provided enantiomerically pure hydrocarbon (+)-**36**.

As the routine measurement of specific rotation of synthetic, enantiopure **36** revealed a reasonably large specific rotation $[\alpha]_D^{25}$: +13.1, ORD seemed one of the viable options to assign the AC. The specific rotations of the five conformers of (*R*,*R*)-**36** were computed at B3LYP/6-311++G(2d,2p) at six different wavelengths (633, 589, 546, 436, 405, and 365 nm). This revealed that only the most populated conformer **36-I** has a negative $[\alpha]_D^{25}$, while all others are positive (Figure 10C). Taking into account the Boltzmann distribution derived from relative free energies at M*P*2/*cc*-pVTZ, we found for (*R*,*R*)-**36** positive

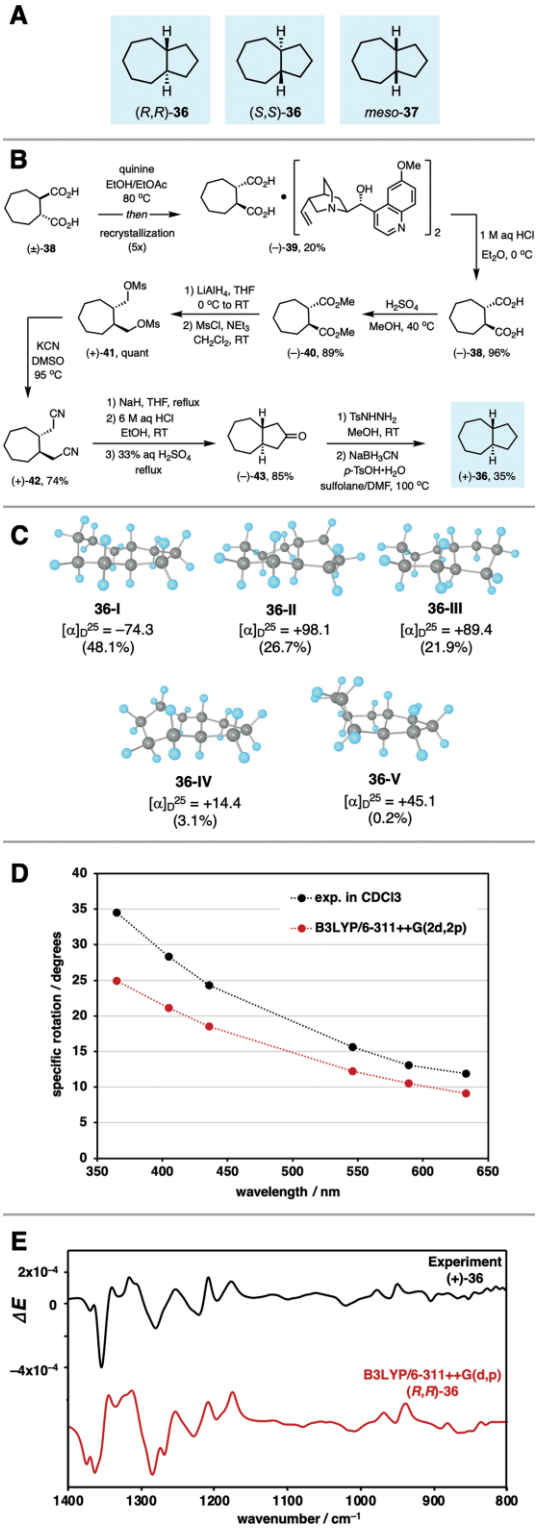


Figure 10. (A) Stereoisomers of perhydroazulene. (B) Synthesis of enantiopure *trans*-perhydroazulene (**36**). (C) Five conformers of (*R*,*R*)-**36** and their specific rotations ($[\alpha]_D^{25}$) computed at B3LYP/6-311++G(2d,2p). The Boltzmann distribution at 298 K computed at M*P*2/*cc*-pVTZ in parentheses. (D) AC determination of **36** by ORD. (E) AC determination of **36** by VCD. The ORD curve and the VCD spectra were adapted with permission from ref.[86] Copyright 2020 American Chemical Society.

and increasing specific rotations $[\alpha]^{25}$ with decreasing wavelengths. The measurement of specific rotations of synthetic **36** clearly showed these features (Figure 10D) and we tentatively assigned the AC as (*R*,*R*)-(+)-**36**. To solidify this assignment, we moved on to VCD spectroscopy. To simulate the VCD spectrum, we again considered the Boltzmann distribution of the relevant conformers. In the spectroscopically viable region of 1400–800 cm^{-1}, the experimental and computed VCD spectra of (+)-**36** and (*R*,*R*)-**36**, respectively, are in excellent agreement (Figure 10E), which confirms that the AC of (+)-**36** is indeed (*R*,*R*). The assignment based on the ORD and VCD techniques was consistent with that derived from single-crystal X-ray diffraction analysis of (–)-**39**.

4. Emerging Methods for AC Determination

Despite the demonstrated successes in AC determination, none of the analytical methods are without limitations and new methods are being actively developed. Two emerging approaches, namely, microscopic techniques and the crystalline sponge method, are particularly promising methods for AC determination.

4.1. Microscopic Techniques

In Pasteur's classic experiment, differentiation and separation of the two enantiomers of sodium ammonium tartrate were achieved by visual inspection of tweezer-separated enantiomorphic crystals with a magnifying glass[89a]. In recent times, advances in scanning probe microscopies (SPMs) have enabled stereochemical analysis and manipulation of chemical substances at the atomic or single-molecule level. Scanning tunneling microscopy (STM) – the first SPM invented by two IBM researchers, Binnig and Rohrer[89b] – has been utilized for AC assignments of 2-butene chemisorbed on a silicon surface (on-surface chirality)[90] and 2-bromohexadecanoic acid adsorbed on graphite.[91] In a recent fascinating study, Ernst performed Pasteur's experiment at the single-molecule level: self-assembled heterochiral dimers of heptahelicene were separated on a copper surface and the chirality of each composite monomer was subsequently identified.[92] Atomic force microscopy (AFM) is another common SPM and was also invented by Binnig.[93] STM relies on tunneling current between the tip and surface and only applicable to conductive surfaces; on the other hand, AFM utilizes repulsive (in the contact mode) or attractive (in the non-contact mode) atomic force and has a broader scope of analyte substances. AFM was utilized to identify the chirality of mostly planar polyaromatic products of on-surface chirality transfer reactions.[94] In another study, AFM enabled the visual inspection of dimers, trimers, and tetramers of heptahelicene to identify the handedness of composite monomers.[95] Although these examples illustrate the unique power of SPMs, stereochemical assignments of polyaromatic compounds can be rather easily determined by other techniques such as ORD and ECD owing to the presence of photochromic groups.

In 2018, we demonstrated the application of low-temperature AFM with a CO-functionalized tip to visualize single molecules of [123]tetramantane (**29**, vide supra) that has no photochromic groups for ORD and ECD measurements (Figure 11).[96]

The AC assignment was enabled by differentiation of the two enantiomers along with their orientations on a Cu(111) surface by visualizing characteristic hydrogens. In addition to the very low surface temperature (15 K), no need for a particular atom, functional group, and chromophore makes this technique potentially applicable even to volatile alkanes.

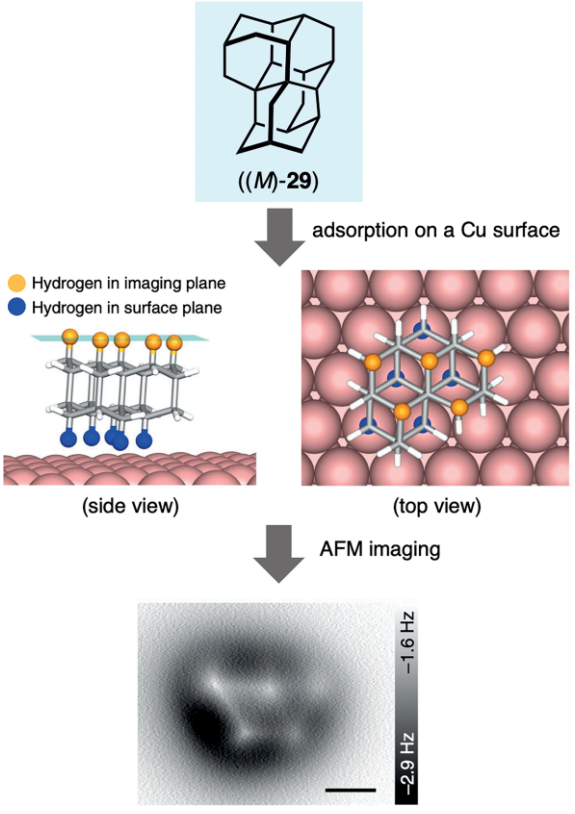


Figure 11. Visual inspection of individual (*M*)-[123]tetramantane ((*M*)-**29**) by the AFM technique. Figures were reprinted from ref.[96]

4.2. The Crystalline Sponge Method

Although the single-crystal X-ray diffraction technique is currently the most powerful method for AC determination, the requirement for single crystals is a serious problem. When the samples are oily materials or available in very small quantities only, one must rely on other methods. The need for heavy atom(s) in the structure also limits the substrate scope of the method.

In 2013, Fujita introduced a revolutionary technique coined "the crystalline sponge method".[97] In this method, guest molecules of unknown AC are soaked into porous metal complexes, e.g., metal-organic frameworks (MOFs), before the acquisition of an X-ray crystal structure, thereby eliminating the need for crystallization of the samples. As the framework, $[(ZnI_2)_3(tpt)_2(solvent)_x]$ (tpt = 2,4,6-tris(4-pyridyl)-1,3,5-triazine), contains heavy atoms (i.e., Zn and I), anomalous dispersion of these atoms present in the host framework can be utilized to determine the AC of the guest molecule (i.e., there is no need for a heavy atom in the guest molecule). An important limitation of the method is the lability of the host framework to Lewis bases in solvents and guest molecules though some improvements have been made using milder soaking conditions and/or $ZnCl_2$ as the metal component.[98]

The crystalline sponge method has been utilized for AC determination of a variety of challenging organic compounds including small molecules with a quaternary carbon stereogenic center,[99] with planar or axial chirality,[100] and with volatile alkenes.[101] Remarkable applications for AC determination of natural products include the hydrocarbon astellifadiene (**44**)[102] and the pseudo-meso compound elatenyne (**45**)[103] shown in Figure 12. Although the applicability to chiral alkanes has yet to be seen, the crystalline sponge method is a promising analytical technique with broad substrate scope.

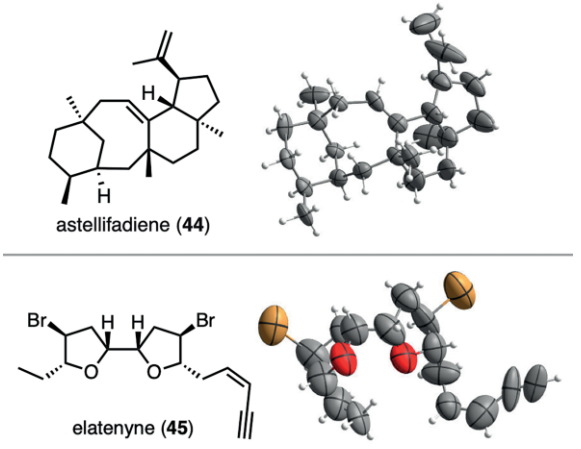
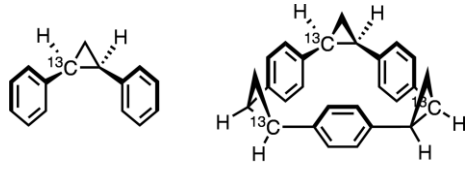


Figure 12. AC determination of astellifadiene (**44**) and elatenyne (**45**) by the crystalline sponge method. Thermal ellipsoids are set at the 50% probability level.

5. Summary and Outlook

We present a survey of methods for AC determination of chiral organic molecules, namely, single-crystal X-ray analysis, Mosher NMR analysis, ORD, ECD, VCD, and ROA spectroscopy with their respective scopes and limitations. We demonstrate our efforts in determining the absolute configuration of chiral alkanes by judiciously selecting appropriate analytical techniques. Murakami and co-workers recently documented the synthesis of hydrocarbons **46** and **47** (Figure 13).[104] The chirality of these molecules is only due to the asymmetric arrangement of $^{12}C/^{13}C$ atoms and exhibit essentially no optical rotation. In their study, the group succeeded in AC determination of these challenging hydrocarbons employing VCD spectroscopy combined with DFT computations. This together with the examples presented in this Minireview manifest that today's better accessibility to (high-level) quantum chemical computations significantly facilitates AC assignment of many (even challenging) chiral molecules by means of chiroptical spectroscopy (ORD, ECD, VCD, and ROA). Tedious compound derivatizations and total syntheses using a material of known AC may already be considered obsolete.



46 47

Figure 13. Crypto-optically active hydrocarbons whose ACs were recently studied by Murakami.

In the future, we firmly believe that microscopic techniques will be one of the standard tools for AC determination. Imagine that a complex natural product is adsorbed on a surface and the multiple stereogenic centers are assigned all at once. It may be even possible to visualize the structure of a chiral molecule via the 3D printed model while the AFM tip scans the sample surface. With further technological advances, we may witness organic chemistry laboratories where such an approach is routine.

Acknowledgments

This work was supported by the Alexander von Humboldt Foundation (postdoctoral fellowship to F.S.). Open access funding enabled and organized by Projekt DEAL.

Keywords: Alkanes · Analytical methods · Chirality · Configuration determination · Structure elucidation

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Received: May 20, 2020