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Letter

Absolute Configuration of *trans*-Perhydroazulene

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ABSTRACT: We present the absolute configuration (AC) determination of an alkane, <i>trans</i> -perhydroazulene (1), that displays the naturally very common trans fused $[5,7]$ ring system. We outline the first synthesis yielding enantiopure 1 and the application of optical rotatory dispersion (ORD) and vibrational circular dichroism (VCD) techniques. The spectroscopic results are	H H H
In excellent agreement with the computed ORD at $B3LYP/6-311++G(2d,2p)$ and the computed VCD spectrum at $B3LYP/6-311++G(d,p)$, providing an assignment of the AC as $(R,R)-(+)-1$.	 first synthesis in enantiopure form absolute configuration determination by chiroptical spectroscopies

N otwithstanding the fact that the absolute configuration (AC) of organic molecules is of prime importance for their properties and functions, its determination is often an elaborate task. The assignment of the AC of alkanes, which represent the parent systems of many natural products, is particularly challenging because of their chemical inertness and conformational flexibility and the absence of photochromic groups. Bijvoet's anomalous dispersion technique in single-crystal X-ray structure analysis requires the presence of heavy atom(s).^{1,2} Mosher's NMR method needs an alcohol or amine in the molecule for derivatization into a pair of diastereomeric esters or amides with enantiopure Mosher acids.^{3,4} The installation of such an atom or functional group to alkanes is, however, synthetically challenging, especially without affecting stereogenic centers.

Chiroptical methods such as vibrational circular dichroism (VCD),^{5,6} Raman optical activity (ROA),⁷ and optical rotatory dispersion (ORD)⁸ are powerful methods for the assignment of ACs by matching experimentally measured and computed spectra. The implementation of ROA⁹ and VCD¹⁰ to the AC determination of a crypto-optically active¹¹ (sometimes also known as cryptochiral, a misnomer)¹² alkane, hexadeuterated neopentane [C(CH₃)(CH₂²H)(CH²H₂)(C²H₃)], is a perfect illustration of the power of chiroptical spectroscopies matched with theory.¹⁰

Recently, we disclosed the synthesis of racemic (chiral) *trans*-perhydroazulene (1) and *meso*- (achiral) *cis*-perhydroazulene (2) along with a conformational analysis (Figure 1).¹³ The key finding was the higher stability of the cis isomer at ambient temperatures. Our motivation to study 1 and 2 was their structural importance in many terpene natural products.^{14–16} Hence, it intrigued us that 1 has not been prepared in the enantiopure form and that the AC of 1, the parent structure of all perhydroazulene terpenoids, is unknown. Herein we document the AC determination of 1 enabled by the synthesis of enantiopure 1 and structure analyses

employing ORD and VCD spectroscopies, both of which assigned the AC of (+)-1 as (R,R). Further evidence of the assigned AC was provided by the X-ray crystallographic analysis of a key synthetic intermediate for 1. The aim of our study is not merely the assignment of the AC of 1 but also the illustration that this can be done with high confidence for a synthetically relevant saturated hydrocarbon skeleton that is devoid of functional groups.



Figure 1. Stereoisomers of parent perhydroazulenes 1 and 2.

We began with the preparation of enantiomerically pure 1. Our initial attempts to separate the two enantiomers of 1 by chiral HPLC were unsuccessful; without polar functional groups, 1 hardly interacts with a chiral stationary phase to allow chiral discrimination. Thus we turned our focus to the synthesis of 1, as depicted in Scheme 1. Following a literature procedure,¹⁷ we prepared racemic *trans*-cycloheptane-1,2-dicarboxylic acid (4) on a decagram scale using cycloheptanone (3) as the starting material.

The resolution of (\pm) -4 has been rare; we found only two examples reported independently by Raphael¹⁷ and Sicher¹⁸

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Scheme 1. Synthesis of Enantiopure 1



nearly 60 years ago, where brucine and quinine, respectively, were used as resolving agents. Although resolved dicarboxylic acid 4 was optically active, the enantiopurity had not been determined. It turned out that the resolution with quinine worked well, and after five recrystallizations of (-)-5, the enantiopurity of (-)-4 reached 99% *ee.* (See the SI for experimental details.) We also performed the resolution of (\pm) -4 with brucine; however, the result was not reproducible, and crystalline dibrucine salts were not obtained.

With the chiral resolution complete, we proceeded with the decomposition of diquinine salt (-)-5 followed by conversion of the free acid to the methyl ester (-)-6. Dimesylate (+)-7 formed by reduction and mesylation was transformed into dinitrile (+)-8.¹⁹ The [5,7]-bicyclic structure was constructed by the Thorpe–Ziegler reaction;²⁰ the crude α -imino nitrile product was subjected to hydrolysis and decarboxylation to give ketone (-)-9. A modified Wolff–Kishner reduction²¹ completed the synthesis of (+)-1.

Chiral alkanes often show very small optical rotations that could lead to unreliable AC assignments.²²⁻²⁴ For 1, however, the specific rotation at the Na D-line (589 nm) is reasonably large: $[\alpha]_D^{25} = +13.1$. This made a comparison between experimental and computed optical rotations a viable option to assign the AC. $^{11,25-28}$ Accordingly, we computed specific rotations of the five conformers of 1 (1-I to 1-V, Figure 2A) in the gas phase at six wavelengths (633, 589, 546, 436, 405, and 365 nm) at B3LYP/6-311++G(2d,2p). The conformers have very different specific rotations, emphasizing the sensitivity of these values on small geometric changes. Notably, only the most populated conformer 1-I has a negative $[\alpha]_D^{25}$, whereas all others are positive. Our previous studies demonstrated that the computed thermochemistry data of 1 at MP2/cc-pVTZ agree well with experimental data.¹³ Thus, on the basis of the relative free energies at 298 K computed at this level of theory, we calculated Boltzmann-averaged specific rotations of both enantiomers of 1. This revealed that for (R,R)-1, $[\alpha]_D^{25}$ is positive, and its specific rotation should increase with decreasing wavelengths.²⁹ In fact, the measurements of specific rotation at varying wavelengths clearly show these features (Figure 2B), and we tentatively assigned our synthetic compound as (R,R)-(+)-1. Although there was better agreement between the measured and computed ORDs following the previously described procedure, the same AC assignment resulted when Boltzmann-averaged specific rotations were calculated based on the relative free energies at B3LYP/6-311+ +G(2d,2p) (Figure S2).



Figure 2. Assignment of the AC of **1** based on specific rotations. (A) Five conformers of (R,R)-1 and their specific rotations $([\alpha]_D^{25})$ computed at B3LYP/6-311++G(2d,2p). The Boltzmann distribution at 298 K computed at MP2/cc-pVTZ is in parentheses. (B) Experimental (black, 298 K) and computed (red, 298 K) specific rotations at different wavelengths.

Next, VCD spectroscopy was implemented to solidify our AC assignment of 1. Because all chiral molecules are IR-active, the VCD technique has been successfully utilized for the AC determination of numerous organic molecules,³⁰ including alkanes.^{10,27,28,31}

We first measured the IR spectrum of (+)-1 and compared it with the Boltzmann-averaged spectrum computed at B3LYP/ 6-311++G(d,p). Again, for the reason that the MP2/cc-pVTZ computations provided accurate thermochemical data of 1,¹³ the Boltzmann distribution derived from the relative free energies (298 K) computed at this level was applied to generate the computed IR spectrum. The agreement between the experimental and computed IR spectra verified that B3LYP/6-311++G(d,p) is appropriate to compute IR and VCD spectra (Figure 3A). We measured the VCD traces of



Figure 3. Assignment of the AC of **1** by VCD. (A) Experimental (neat; black) and computed (B3LYP/6-311++G(d,p); gas phase, 6 cm⁻¹ simulated line width, scaled by 0.98; red) IR spectra of **1**. (B) Experimental (neat; black) and computed (B3LYP/6-311++G(d,p); gas phase, 8 cm⁻¹ line width, scaled by 0.98; red) VCD spectra of (+)-**1** and (*R*,*R*)-**1**, respectively.

(+)-1 and, for baseline corrections and the elimination of systematic errors, also that of (\pm) -1. Figure 3B shows the experimental and computed (B3LYP/6-311++G(d,p), scaled by 0.98) VCD spectra of (+)-1 and (*R*,*R*)-1, respectively, in the spectroscopically viable region of 1400-800 cm⁻¹. The excellent agreement confirms that the AC of (+)-1 is indeed (*R*,*R*).

Finally, X-ray crystallographic analysis provided further evidence of our AC determination of 1 on the basis of single crystals of diquinine salt (–)-5 (Figure 4). Because the AC for quinine is known, the AC of resolved dicarboxylic acid (–)-4 was assigned to (S,S). Because our synthetic route does not involve transformations that affect the two adjacent stereogenic centers, the AC of our synthetic (+)-1 must indeed be (R,R).

Even today, many chemists execute AC assignments by means of laborious compound derivatizations and total syntheses using a material of known AC. As demonstrated here, such synthetic efforts only for the purpose of AC determination are not necessary; we synthesized enantiomerically pure 1 only because of the extreme difficulty to separate the two enantiomers. Our results showcase that chiroptical spectroscopies combined with readily executed computations are reliable approaches to the AC determination of even the most challenging and fundamental organic molecules. Because conformationally flexible alkanes often belong to a class of crypto-optically active compounds whose ACs are extremely difficult to determine, the unambiguous assignment of the AC of 1, consisting of multiple conformers, is comforting.

Note that (R,R)-(+)-1 is an oily material; in fact, chiroptical spectroscopies could be the only methods currently available to determine the AC of molecules in such physical states. There are two emerging technologies that rival chiroptical



Figure 4. Molecular structure from the X-ray analysis of diquinine salt (-)-5. Only hydrogens at the stereogenic centers and those forming ionic hydrogen bonds (in orange) are shown. A cocrystallized water molecule was omitted for clarity. Thermal ellipsoids are set at the 50% probability level.

spectroscopies: The first is the crystalline sponge method developed by Fujita and coworkers,³²⁻³⁹ although the applicability of the method to alkanes has yet to be seen. The second technique is the visual inspection of single molecules by microscopic techniques such as scanning tunneling microscopy $(STM)^{40-43}$ and atomic force microscopy (AFM).^{44,45} We recently demonstrated that low-temperature AFM with a CO-functionalized tip provided images of individual [123]tetramantane—a chiral, rigid alkane consisting of four adamantane units—adsorbed on a copper surface.⁴⁴ The approach differentiated the two enantiomers along with their orientations on the surface and enabled the AC assignment by direct visualization of the single molecules. Because the surface temperature is as low as 15 K, even volatile compounds such as 1 can be suitable analytes for this method. Our next step will be the visualization of single molecules of 1 to further expand the scope of our AFM-based AC assignment.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01184.

Full experimental procedures, compound characterization, X-ray crystallographic data, and computational details (PDF)

Accession Codes

CCDC 1988737 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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