P Chiral Discrimination Very Important Paper

Synthesis and Stereochemical Assignment of Crypto-Optically Active ²H₆-Neopentane

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Dedicated to Professor Duilio Arigoni

Abstract: The determination of the absolute configuration of chiral molecules is at the heart of asymmetric synthesis. Here we probe the spectroscopic limits for chiral discrimination with NMR spectroscopy in chiral aligned media and with vibrational circular dichroism spectroscopy of the sixfold-deuterated chiral neopentane. The study of this compound presents formidable challenges since its stereogenicity is only due to small mass differences. For this purpose, we selectively prepared both enantiomers of ${}^{2}H_{6}$ -1 through a concise synthesis utilizing multifunctional intermediates. While NMR spectroscopy in chiral aligned media could be used to characterize the precursors to ${}^{2}H_{6}$ -1, the final assignment could only be accomplished with VCD spectroscopy, despite the fleetingly small dichroic properties of 1. Both enantiomers were assigned by matching the VCD spectra with those computed with density functional theory.

he creation of new molecular entities and subsequent exploitation of their properties is central to a broad spectrum of research disciplines ranging from medicine to materials. One of these important properties, overlapping many branches in the sciences, e.g., chemistry, physics, and mathematics, is a symmetry property called chirality. Molecules are chiral if they cannot be superimposed on their miror images. The absolute configuration of enantiomers, defined either as "R" (rectus) or "S"(sinister) according to the Cahn–Ingold– Prelog (CIP) rules, determines the direction in which an enantiomer rotates the plane of polarized light, namely "+"

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201505349. (clockwise) or "-" (counterclockwise) optical rotation.^[1] However, in some very special cases of chirality, due to the electronic properties of the chiral molecule, the optical rotation is not measurable.^[2] The determination of the absolute configuration of these cryptochiral^[3]—better called crypto-optically active^[4]—compounds remains therefore extremely challenging. For instance, a suitable prototype of a crypto-optically active molecule is appropriately deuterated neopentane (excluding its carbon isotopologues), C(CH₃)- $(CH_2^2H)(CH^2H_2)(C^2H_3)$, henceforth referred to as ${}^{2}H_{6}$ -1, which is the smallest chiral compound possessing a quaternary carbon stereogenic center. This crypto-optically active molecule owes its chirality exclusively to an asymmetric distribution of the masses of the nuclei, whilst having virtually the same electron distribution as all-¹H-neopentane.^[5] As a matter of fact, within the commonly invoked Born-Oppenheimer (BO) approximation, ${}^{2}H_{6}$ -1 is electronically achiral and BO computations of its optical rotation return a zero value. Even dynamic computations beyond the BO approximation deliver, at best, vanishingly small values that could not be measured reliably.^[6] The preparation as well as the experimental assignment of the absolute configuration of the enantiomers of ${}^{2}H_{6}-1$ therefore poses a formidable analytical challenge and was (so far) exclusively achieved for its R enantiomer through matching of the experimentally determined Raman optical activity (ROA) spectra with density functional theory (DFT) computations.^[7] Following these elegant studies, a complementary technique would be vibrational circular dichroism (VCD) spectroscopy, whose application to both enantiomers of ²H₆-1 has been examined theoretically but not yet experimentally. When using VCD, several questions arise. For instance, could one discern the individual contributions of the nine possible conformers of ${}^{2}H_{6}$ -1 that present minima (i.e., rotamers) on the corresponding rotational potential energy surface (PES) to the VCD spectra? Is it possible to match the spectra with quantum mechanical computations to assign absolute stereochemistry? On the basis of such computations it was concluded that the contributions of the individual rotamers would very significantly reduce the overall VCD intensities but should in principle, although not yet demonstrated, be measureable in the 700–1400 cm⁻¹ range.^[5]

As the assignment of absolute configurations of chiral molecules is in principle more reliable with ROA and VCD techniques than with CD and optical rotatory dispersion (ORD) alone,^[8] it is essential to determine whether current

experimental and theoretical approaches can indeed be trustworthy to the degree that they can replace the (current) ultimate proof of stereochemical identity, namely the synthesis of a target structure from a natural product with established absolute configuration, a very tedious and timeconsuming strategy.

Another alternative for spectropically separating the signals of enantiomers of ${}^{2}\text{H}_{6}$ -1 should be NMR experiments using deuterium as a nuclear probe and chiral liquid crystals (CLC) as oriented NMR solvents. This approach ideally complements vibrational spectroscopy, even if the determination of the absolute configuration (of chiral molecules with a single-stereogenic center) is impossible, without the a priori knowledge of the Saupe's order tensors.^[9] It has never been utilized for a chiral molecule as challenging as ${}^{2}\text{H}_{6}$ -1, and is, as we will demonstrate, not yet capable of spectral enantiodiscrimination of an essentially unfunctionalized molecule such as ${}^{2}\text{H}_{6}$ -1.

Our strategy for the preparation of both enantiomers of ${}^{2}\text{H}_{6}\text{-1}$ (Scheme 1) was to promote the transformation of the easily accessible ω -ene cyclopropanes^[10] as well as alkylide-necyclopropanes^[11] into acyclic molecular fragments by



Scheme 1. Synthesis of $(S)^{-2}H_{6}$ -1.

merging two modes of chemical activation.^[12] Indeed, through the use of a unique organometallic species, successive allylic C–H bond activations followed by a selective C–C bond cleavage and selective functionalization with two different electrophiles,^[10] complex molecular architectures possessing a quaternary carbon stereogenic center^[13] were readily constructed from common starting materials.^[14,15] We therefore predicted that the control of both modes of activation could be successfully used for the direct and expedient preparation of both (*R*)- and (*S*)-**1** from the easily accessible, enantiomerically enriched alkylidenecyclopropane (²H₃-**2**, Scheme 1, e.r. 98:2).^[16]

The enantiomeric ratio of enantioenriched ${}^{2}H_{3}$ -2 was determined using proton-decoupled deuterium NMR (${}^{2}H{-}{{}^{1}H}$) techniques using a polypeptide lyotropic CLC made of poly- γ -benzyl-L-glutamate (PBLG) and chloroform as an organic aligning NMR solvent,^[17] whereas the absolute configuration was determined by analogy to our previous work.^[11] This NMR approach dedicated to the determination of enantiopurity is based on the difference of residual quadrupolar couplings (RQC) of an enantiomeric pair,

 $\Delta v_{\rm O}(R) \neq \Delta v_{\rm O}(S)$, when nuclei of spin I = 1 (such as deuterium) are used as nuclear probes.^[17] Due to the high sensitivity of the quadrupolar interaction (H_0) to small variations of ordering of the C-D vector, the method is particularly efficient in discriminating between enantiomers of chiral molecules (isotopically enriched or at natural-abundance deuterium level), including compounds that are chiral by virtue of isotopic substitution such as 2.^[18-20] The presence of two quadrupolar doublets ($|\Delta v_0| = 8$ and 15 Hz) in the ²H-{¹H} spectrum of (\pm) -²H₃-**2** recorded in the CLC shows that spectral discrimination does occur (Figure 1A, top); the determination of peak surfaces performed by deconvoluting the ²H signals in the enantioenriched series indicate that the enantiomeric ratio is higher than 98:2 (Figure 1A, bottom). When $(S)^{-2}H_{3}-2$ is treated with the Negishi reagent,^[21] the combined zirconocene-mediated allylic C-H bond activation followed by selective C-C bond cleavage and deuteration of the resulting bismetalated species with ${}^{2}\text{H}_{3}\text{O}^{+}$ gives (R)- ${}^{2}\text{H}_{5}$ -3 on gram scale in 91% yield. As the stereogenic quaternary center is at no risk of racemization in the process, the optical purity is identical throughout the rest of the synthesis (Scheme 1). Subsequent oxidative cleavage of the double

bond followed by the in situ reduction with NaBD₄ leads to the volatile neopentanol which must be protected in situ to give the tosylate adduct (R)-²H₅-4 in 89 % yield. The final reduction was performed with LiAl²H₄ in Oct₂O to give the expected gaseous (S)-²H₆-1 in quantitative yield. The opposite enantiomer (R)-²H₆-1 was similarly prepared from the alkylidenecyclopropane (R)-²H₃-2.^[16]

The structure of ${}^{2}\text{H}_{6}\text{-1}$ was definitively established by ${}^{2}\text{H}$ NMR spectroscopy with and without proton decoupling in an isotropic solvent (Figure 1 B, top and bottom). Thus, the presence of three ${}^{2}\text{H}$ resonances in the ${}^{2}\text{H}\text{-}{}^{1}\text{H}$ 1D spectrum with a relative intensity of 3:2:1 indicates the discrimination of mono-, di-, and trideuterated methyl groups on the basis of their ${}^{2}\text{H}$



Figure 1. A) Determination of the e.r. of ${}^{2}H_{3}$ -**2** by ${}^{2}H$ -{ ${}^{1}H$ } NMR analysis (14 T/cryoprobe) in the chiral liquid crystal PBLG (top: racemic series; bottom: enantiomerically enriched series). B) ${}^{2}H$ assignment (δ and J) of ${}^{2}H_{6}$ -**1** in liquid (pyridine). Note the scalar coupling patterns when ${}^{1}H$ decoupling is off (bottom).

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chemical shifts $\delta(^{2}\text{H})$. This assignment is also unambiguously confirmed by the ²H fine structures (a triplet, a doublet, and a singlet, centered at 0.793, 0.785, and 0.755 ppm in pyridine, respectively) due to intramethyl geminal ${}^{2}H{-}^{1}H$ scalar (J) couplings when the ¹H decoupling is turned off (see also the Supporting Information). Considering the positive results for the determination of the enantiomeric ratio of $(S)^{-2}H_{3}$ -2, and previous studies on isotopic enantiodiscrimination,^{[19] 2}H-{¹H} NMR in PBLG mesophases, we applied the same technique again to differentiate the enantiomeric signals of (rac)-²H₆-1, with the goal of assessing the enantiopurity of enantioenriched (S)-²H₆-**1**. Interestingly, small but spectrally resolved quadrupolar doublets ($|\Delta v_0| < 2 \text{ Hz}$) associated with the mono- and dideuterated methyl groups (see the Supporting Information) indicate that this asymmetric (C_1 point group) molecule is slightly oriented in this weakly aligning lyotropic chiral mesophase. Unfortunately, all attempts to discriminate the enantiomers based on RQC differences failed, irrespective of the temperature (in a range of 30 K) and the polarity of the cosolvent (CHCl₃ or pyridine). It appears that the overall shape recognition mechanisms involved in the chiral discrimination phenomenon^[22] are in the case of PBLG unable to differentiate the extremely small topological differences between the mono-, di-, and trideuterated methyl groups around the stereogenic carbon atom of ${}^{2}H_{6}$ -1.

From the perspective of the CDP, the absence of visible discriminations in this challenging example emphasizes the limits of efficiency of overall shape recognition mechanisms with this particular chiral liquid crystals.^[23] The challenging assignment of the absolute configuration of (S)-²H₆-**1** thus at this time directly relies on the combination of highly sensitive vibrational spectroscopy with high-level theory.

The experimental infrared (IR) spectrum of ${}^{2}H_{6}$ -1 agrees well with the spectrum computed at the CCSD(T)/-cc-pVTZ level of theory (unscaled, Figure 2A; see Figure S5 for enlarged details), which is considered the "gold standard"^[24] of currently available ab initio methods. Note that the nine rotamers have approximately equal statistical weight^[5] as their energy difference at this level amounts to less than 10⁻⁴ kcalmol⁻¹ only due zero-point vibrational energy contributions. As the rotational barrier in 1 derived from IR measurements in the crystalline state^[25] or in the gas phase^[26] only amounts to 4.3 kcalmol⁻¹, the nine conformers of ${}^{2}\text{H}_{6}$ -1 must be essentially equally populated in the gas phase at room temperature. The computed rotational barrier only amounts to 3.7 kcal mol⁻¹ at CCSD(T)/cc-pVTZ//B3LYP/augcc-pVTZ + ZPVE. Such a relatively small rotational barrier implies that at 0-25 °C there is essentially free internal rotation.

Despite the large and readily discernible IR signals in the C-H/²H absorption region, the B3LYP/aug-cc-pVTZ computed VCD spectrum of (S)-²H₆-**1** (simulated with 3 cm⁻¹ linewidth) is remarkably poor in terms of spectroscopic features (Figure 2B), as predicted.^[5] In the range of about 1500–3000 cm⁻¹ virtually all signal intensities of the nine rotamers cancel so that there is essentially no VCD signal in this range and one is left with the typically less intense and less well resolved fingerprint region. An additional challenge is the fact that ²H₆-**1** is a good Raman scatterer but a rather poor



Figure 2. A) Computed (CCSD(T)/cc-pVTZ; orange) and experimental matrix IR spectrum (Ar, 8 K; black) of (S)-²H₆-1. B) Spectral region for VCD measurements of ²H₆-1. C) Cancellation of VCD signals of the nine (S)-²H₆-1 rotamers. D) Matching of experimental VCD (Ar, 8 K; black) and computed (B3LYP/aug-cc-pVTZ, 3 cm⁻¹ linewidth; orange) VCD spectrum of (S)-²H₆-1 (difference of (S)- and (R)-²H₆-1 VCD traces).

IR absorber.^[5] As a consequence, the range left accessible for VCD measurements of $1000-1500 \text{ cm}^{-1}$ is of very low intensity because a larger number of signals with opposite contributions to the total intensity coincide (for a color-coded

distribution of the individual rotamers see Figure 2 C), leading to reduced total band intensities. All of this poses major challenges on compound purity and handling, and the required spectral resolution.

We sought to counteract this problem by employing the matrix isolation technique, in which the target compound is isolated in a dilute and rigid matrix of a gaseous host material under cryogenic conditions. Both the absence of intermolecular interactions, owing to the high dilution of the isolated species, as well as the very low temperature usually below 15 K afford narrow signal profiles, which greatly aid spectroscopic investigations. This advantage is, however, slightly diminished due to the lower concentration of the target compound in matrix environment, so that great care has to be taken to determine the optimal conditions for VCD experiments.

Indeed, we note the vanishingly small absorbance values in Figure 2D of only about 10⁻⁵ absorbance units in our experiments, in which both enantiomers of ${}^{2}H_{6}$ -1 were isolated in Ar at only 8 K. To be able to discern individual signals for the low-intensity spectrum of the S enantiomer, we subtracted from it the VCD trace of the R enantiomer, thereby increasing the signal-to-noise ratio and hence the overall quality; alternatively, we subtracted from the VCD traces of the S and R enantiomers, respectively, the VCD trace of $(rac)^{-2}H_{6}$ -1 as the baseline. The resulting VCD spectra (see Figure S6) indeed appear as mirror images. The agreement between experiment and theory of all acquired spectral data both in the IR and VCD spectra is remarkably good and warrants the assignment of the absolute configurations of both enantiomer by comparison with the computed VCD spectra.

Despite the earlier notion that "Vibronic effects in the vacuum ultraviolet circular dichroism might reveal that the molecule is chiral, but the presence of nine rotamers would make it extremely difficult to interpret the spectra, because the spatial arrangement of the rotamers' nuclei resembles that of enantiomers...",^[7] we clearly point out here that the assignment of even one of the most challenging chiral molecules can be successfully achieved through a combination of sophisticated experimental and theoretical techniques. As such, the title structure with an essentially centrosymmetric electron distribution and multiple close-lying rotamers whose optical activities almost perfectly cancel is a stringent test case for the current arsenal of experimental and theoretical methods available for the determination of structures and absolute configurations of chiral molecules.

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